Treatment Options for Glioblastoma and other Gliomas

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Since my own diagnosis of glioblastoma (GBM) in 1995 at age 50, I have spent considerable time researching the literature for treatment options, and the following discussion summarizes what I have learned. Most of the information is from medical journals. Some is from information that has been contributed by others to various online brain tumor patient support groups, which I have followed up on, and some is from direct communications by phone or e-mail with various physicians conducting the treatments that are described. References are presented at the end for those who would like their physicians to take this information seriously. Although this discussion is intended to be primarily descriptive of the recent development of new treatment options, it is motivated by my belief that the development of new agents, per se, is likely to fall short of providing effective treatment. What is needed, in addition, is a new approach to treatment that recognizes the power of evolution as the enemy of victims of cancer. Some specific recommendations for a treatment plan are presented at the end of the article.

A more extensive account of my philosophy of treatment, and the reasons for it, are provided in my (2002) book, 'Surviving "Terminal" Cancer: Clinical Trials, Drug Cocktails, and Other Treatments Your Doctor Won't Tell You About'. It can be ordered elsewhere on this website, from Amazon.com, from your local bookstore, or directly from the publisher:

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When I began my own search for effective treatments, the options that were available offered little chance for surviving my diagnosis. The standard treatment included surgery, radiation, and nitrosourea-based chemotherapy, either BCNU alone or CCNU combined with procarbazine and vincristine (known as the PCV combination). While this treatment has worked for a small minority of people, its 5-year survival rate has been only 2-5%. Median survival has been about a year, which is 2-3 months longer than for patients receiving radiation alone without chemotherapy. Fortunately, as will be discussed in the next section, the past four years has produced a new "gold standard" of treatment for patients newly diagnosed, the combination of radiation with a new chemotherapy agent, temozolomide (trade name temodar in the USA and temodal elsewhere in the world). While this new standard appears to produce a notable improvement in outcome from previous treatments, it still falls far short of being effective for the great majority of patients. What is needed, therefore, is a new philosophy of treatment that goes beyond rigidly defined protocols to include a variety of different agents used in combination.

There are three general premises to the approach to treatment that will be described. The first of these is borrowed from the treatment approach that has evolved in the treatment of AIDS. Both viruses and cancer cells have unstable genetic structures very susceptible to mutations.. This implies that unless a treatment is immediately effective the dynamics of evolution will create new forms that are resistant to whatever the treatment may be. However, if several different treatments are used simultaneously (instead of sequentially, which is typically the case), any given mutation has a much smaller chance of being successful.

The second premise is that cancer treatments of all sorts are probabilistic in their effects. None of them work for everyone, in part because any given cancer diagnosis is an amalgam of different genetic defects that respond in different ways to any given treatment agent. This is especially true for glioblastomas, which have a multiplicity of genetic aberrations that vary widely across individuals and sometimes even within the same tumor of a given individual. As a result it is common that any given "effective" treatment agent will benefit only a minority of patients, often in the range of 15-40%, but do little if anything for the majority. The result is that the chances of finding an effective treatment increase the more different treatment agents that are utilized. Probabilistic effects can and do summate.

The third general principle is that any successful treatment will need to be systemic in nature because it is impossible to identify all of the extensions of the tumor into normal tissue. Moreover, cancer cells are typically evident in locations in the brain distant from the main tumor, indicating that metastases within the brain can occur, although the great majority of tumor recurrences are within or proximal to the original tumor site. Localized treatments such as radiosurgery may be beneficial in terms of buying time, but they are unlikely to provide a cure. Even if the localized treatment eradicates 99.9% of the tumor, the small amount of residual tumor will expand geometrically and soon will cause significant clinical problems.

Until recently, the only systemic treatment available has been chemotherapy, which historically has been ineffective except for a small percentage of patients. An important issue, therefore, is whether chemotherapy can be made to work substantially better than it typically does. Agents that facilitate or augment its effects are critically important. Such agents are available but not widely used. Also becoming available are new systemic treatments that are much less toxic than traditional chemotherapy. The availability of these treatments raises the possibility that some combination of these new agents can be packaged that is substantially less toxic, yet provides effective treatment based on several different independent principles. Thus, the AIDS-type of combination approach is now a genuine possibility whereas it would not have been ten years ago. Because many of these relatively nontoxic new agents were developed for purposes other than cancer, or for different kinds of cancer, their utilization in the treatment of glioblastomas is "off-label", with the result that many oncologists have been hesitant to prescribe them. Thus, patients themselves need to become familiar with these new agents and the evidence available regarding their clinical effectiveness. It is possible, although by no means proven, that some combination of these new agents offers the best possibility for survival.

Patients may or may not learn about the treatments that will be described from their physicians. To appreciate why this may be, it is important to understand how American medicine has been institutionalized. For most medical problems there is an accepted standard of what is the best available treatment. Ideally this is based on phase III clinical trials in which patients are randomly assigned to receive the new treatment or some type of control condition. Treatments that have been studied only in nonrandomized phase II trials will rarely be offered as a treatment option, even if the accepted "best available treatment" is generally ineffective. What happens instead is that patients are encouraged to participate in clinical trials. The problem with this approach is that most medical centers offer few options for an individual patient. Thus, even though a given trial for a new treatment may seem very promising, patients can participate only if that trial is offered by their medical facility. An even more serious problem is that clinical trials with new treatment agents almost always initially study that agent in isolation, usually with patients with recurrent tumors who have the worst prognoses. For newly diagnosed patients this is at best a last resort. What is needed instead is access to the most promising new treatments, in the optimum combinations, at the time of initial diagnosis.

The Role of Chemotherapy

Although chemotherapy has a long history of being ineffective as a treatment for glioblastoma, a recent large randomized European clinical trial has shown clear benefits of adding the new chemotherapy agent, temozolomide (trade name temodar in the USA. Temodal elsewhere in the world), to the standard radiation treatment (1). One group of patients received radiation alone; the other group received radiation plus temodar, first at low dosages during the six weeks of radiation, followed by the standard schedule of higher-dose temodar for days 1-5 out of every 28-day cycle.). Median survival was 15 months, compared to a median survival of 12 months for patients receiving radiation only, a difference that was statistically significant. More impressive was the difference in two-year survival rate, which was 26% for the patients receiving temodar but only 10% for those receiving only radiation. Similar outcome results were obtained in a smaller nonrandomized study in Germany (2) As a result of these new findings, the protocol of temozolomide presented during radiation is now recognized as the "gold standard" of treatment and is now one of the few treatments for glioblastoma that is FDA approved.

But a two-year survival rate of less than 30% obviously cannot be considered an effective treatment, as the great majority of patients receiving the treatment receive at best a minor benefit, accompanied with significant side effects (although temodar is much better tolerated than previous treatments, especially with respect to the cumulative toxicity to the bone marrow). This raises the issues of how to determine who will benefit from the treatment, and, most importantly how to improve the treatment outcomes.

One approach to determining whether an individual patient will benefit from chemotherapy is simply to try 1-2 rounds to see if there is any tumor regression. The debilitating effects of chemotherapy typically occur in later rounds, at which point there is a cumulative decline in blood counts. The extreme nausea and vomiting most associated with chemotherapy in the mind of the lay public is now almost completely preventable by the new anti-nausea agents, Zofran and Kytril. Marijuana also can be very effective in controlling such effects, and recent research has suggested that is has anti-cancer properties in its own right. Thus, for those patients who are relatively robust after surgery and radiation, some amount of chemotherapy experimentation should be possible without major difficulties.

A significant advance in determining which patients will benefit from temodar was reported by the same research group that reported the definitive trial combining low-dosage temodar with radiation. Tumor specimens from the patients in that trial were tested for the level of activation of a specific gene that determines chemoresistance. More specifically, there is a gene (known as MGMT) that allows the damaged tumor cells to repair themselves, with the result that both radiation and chemotherapy are less effective. Patients whose MGMT gene is inactivated (which occurs in 45% of patients) have a significantly greater chance of responding to temodar than those for whom the gene is still functional (3). For patients with an inactive gene, 2-year survival was 23% for those receiving radiation only, compared to 46% for those who received radiation and temodar together. For those with an active MGMT gene the corresponding numbers were 2% and 14%. This implies that patients should have specimens of tumor tissue taken at the time of surgery tested for the status of the MGMT gene. But it is also important to appreciate that the MGMT gene is only one of several mechanisms by which chemoresistance is mediated.

An alternative way to ascertain the value of chemotherapy for an individual patient is the use of chemo-sensitivity testing for the various drugs that are possible treatments. Such testing requires a live sample of the tumor and thus must be planned for in advance of surgery. Culturing the live cells is often problematic, but at least a half-dozen private companies across the country offer this service. Cost ranges from $1000-$2500, depending on the scope of drugs that are tested. Recent evidence has shown that chemosensitivity testing can significantly enhance treatment effectiveness for a variety of different types of cancer, including a recent Japanese study using chemosensitivity testing with glioblastoma patients (4). In general, when chemosensitivity testing indicates an agent has no effect on a patient's tumor the drug is unlikely to have any clinical benefit. On the other hand, tests indicating that a tumor culture is sensitive to a particular agent do not guarantee clinical effectiveness, but it substantially increases the likelihood that the agent will be beneficial. More information about chemosensitivity testing is presented in a separate article listed in the "noteworthy treatments" section that includes the present paper.

Strategies for improving the "Gold Standard"

Combatting chemoresistance

One approach to making temodar more effective is to directly target the mechanisms underlying temodar resistance.The importance of the MGMT gene noted above has inspired the use of a drug known as 06-benzylguanine (06BG), which depletes the enzyme produced by the gene, thus preventing the repair of the temodar-induced damage to the DNA of the glioblastoma cells. Unfortunately, 06BG also increases the sensitivity of the bone marrow cells to temodar's toxic effects, which implies that using 06BG in combination with temodar is functionally similar to using higher dose of temodar. It may be that careful titration of dosage levels will allow this to be a viable strategy, but at present this protocol, which is still experimental, is problematic.

A second source of chemoresistance comes from glycoprotein transport systems, pump-like mechanisms by which the chemotherapy agent is extruded from the cell body. One of these pump mechanisms utilizes calcium channels, so that calcium channel blockers can interfere with its action, thus allowing the chemotherapy agent longer time to be effective. This is important because chemotherapy is effective only when cells are dividing, and only a fraction of the cell population is dividing at any given time. The longer the chemotherapy remains in the cell, the more likely it will be there at the time of cell division. If the extrusion of the chemotherapy drug could be inhibited, chemotherapy should in principle become more effective. Calcium channel blockers, which include commonly used medications for hypertension such as verapamil, have thus been studied for that purpose (5). Unfortunately, these agents have potent effects on the cardiovascular system, so that dosages sufficiently high to produce clinical benefits usually have not been achievable. However, a recent study (6) did report a substantial clinical benefit for patients with breast cancer with a relatively low dosage (240 mg/day). In addition, the combination of verapamil with tamoxifen (which itself blocks the extrusion by a somewhat different mechanism) may possibly increase the clinical benefit (7). In laboratory studies other calcium channel blockers, especially, nicardipine and nimodipine (8,9) have also been shown to effectively increase chemotherapy effectiveness, and may have direct effects on tumor growth themselves.

A variety of other existing drugs have also been shown to increase the effectiveness of chemotherapy, often by unknown mechanisms. The statin drugs used for the treatment of high cholesterol levels, such as simvastin, have been shown to augment the effects of BCNU in laboratory studies (10), but have not yet been combined with chemotherapy in any reported clinical study. Most recently, a common drug used in the treatment of alcoholism, Antabuse (also known as disulfuram), has been shown in laboratory studies to be a powerful inhibitor of the extrusion pump mechanism, although as yet this has not been studied clinically.(11)

The most promising clinical results for combating chemo-resistance has come from the addition of chloroquine, an old anti-malaria drug, to the traditional chemotherapy agent, BCNU. The rationale of chloroquine's use is that is that it stabilizes cellular DNA and thus prevents the mutations that generate chemo-resistance. In an extended study conducted in Mexico (12, 13, 14) patients received the traditional chemotherapy agent BCNU, with or without a 150-mg daily dose of chloroquine. The results were that patients receiving chloroquine had a median survival time of 25 months, while those receiving BCNU alone had a median survival time of 11 months. The mechanism underlying chloroquine’s effects should be applicable to chemotherapies other than BCNU, so it seems likely that chloroquine should increase the efficacy of temodar and other chemotherapy agents as well.

Optimizing the Schedule of Chemotherapy

The standard schedule for using full-dose temodar is days 1-5 out of every 28-day cycle. The recent large Swiss study described above also added daily temodar during radiation but at a lower dosage, followed by the standard five-day schedule after radiation was completed. A clear rationale for why the standard schedule was selected has never been provided and it has become increasingly questionable whether the standard schedule is in fact optimal. One of the earliest small clinical studies with temodar used a daily schedule instead (15), and produced clinical outcomes seemingly better than those obtained with the standard schedule. To evaluate this issue (and others), it is important to distinguish between the different clinical settings in which temodar has been used. The majority of the data comes from nonrandomized phase II clinical trials in which temodar has been used after some other treatment failed, i.e., with what are known as "recurrent" tumors. Only in the last 2-4years have there been many data in which temodar has been used as the initial treatment.

Considering first the studies with recurrent tumors, the first issue is the selection of an appropriate measure of treatment efficacy. Popular for many years was "tumor response", which is the number of patients whose tumors regressed after treatment initiation. This measure has become increasingly questioned because a number of new treatment agents stop the growth of the tumor rather than killing it directly. Accordingly, an increasingly common alternative measure is the time to tumor progression, with one variant of this measure being the percentage of patients who are progression-free six months after treatment initiation (known as PFS-6). A compilation of statistics from prior phase II studies involving patients with recurrent tumors treated with various different chemotherapy agents produced a PFS-6 value of 15%. In contrast, the use of temodar with a comparable set of patients has produced a PFS-6 value of 21%, when using the standard 5-day schedule of temodar administration. However, an alternative schedule of one week on, one week off (i.e., days 1-7 and 15-21 of a 28 day cycle seems to produce substantially better results (16). Here, with an initial 21 patients, the PFS-6 was 48%. A follow-up report (17) after the number of patients had expanded to 39 yielded a PFS-6 value of 43%, approximately double the 21% value produced by the standard 5-day schedule. The dosage of temodar used in this study was 150 mg/ square meter of body surface. By comparison, the dosage of temodar during the five days of the standard schedule is 200-300 mg/ square meter of body surface.

Additional evidence that the alternating week schedule improves clinical outcome comes from a small randomized study (18) involving patients with tumors recurrent after radiation treatment (but apparently no prior chemotherapy). Median survival for the standard schedule was 14 months, while that for the alternating week schedule was 21 months. Two-year survival rate for the standard 5-day schedule was 10%, while 2-year survival with the alternating week schedule was 40%. The alternating week schedule was also reported to have considerably less hematological toxicity.

The inferiority of the standard schedule has also been demonstrated when temodar has been used as the initial treatment after surgery and radiation (19). Patients received either the standard schedule, the alternating week schedule described above, or a daily schedule in which the dose was 75 mg/ square meter of body surface. The corresponding median survivals were 11.9 months for the standard schedule, 15.7 months for the alternating week schedule, and 29.5 months for the daily schedule. There were corresponding differences in two-year survival rates: 21%, 30%, and 51%, for the standard, alternating week, and daily schedules, respectively. Thus, a change to a daily schedule seems to produce a marked improvement in clinical outcome. There are, however, several caveats. This was not a randomized trial, although this is mitigated somewhat by the relatively large number of patients in each condition (35-50). Secondly, only about half of the patients received radiation in addition to temodar, and there were some differences across the different conditions in the percentages receiving radiation, although this variation was substantially smaller than the variation in clinical outcome. Finally, there have been various reports that the daily schedule used in this study produces substantial amounts of lymphophenia, which substantially increases the risk of various kinds of infections. On the other hand, the authors report that the more typical myelotoxicity (bone marrow suppression) was substantially less than with the alternative two schedules.

Unfortunately, a subsequent study (20), which directly compared the alternating week schedule to the daily schedule has yielded a different conclusion about their relative efficacy. Fifty-one patients received the standard temodar +radiation protocol and then were randomly assigned to the different schedules. Median progression-free survival was 6.8 months for the alternating week schedule but only 3.8 months for the daily schedule. Median survival was also in favor of the alternating week schedule. Interpretation of this study is problematic, however, because the survival statistics, especially for the daily schedule, were substantially inferior to those described above. The result is that there is no clear resolution of the issue of the optimal schedule, although it seems clear that the standard schedule, which is routinely used, is most likely inferior to the other two alternatives that have been studied.

One rationale for using the daily schedule is that such a schedule not only attacks the tumor cells but also prevents the growth of new blood vessels feeding the tumor. Several prominent oncologists have argued that the rationale for the standard practice of periodic administration of the maximum tolerated dosage is based on inadequate experimental data and needs to be reconsidered. They have also reported experimental studies showing that rodents that have become resistant to chemotherapy administered with the usual bolus injections will nevertheless show a clinical response when the same chemotherapy is administered continuously at low dosages (21, 22). Moreover, in comparison to the bolus dosage, continuous low dosages (so-called metronomic chemotherapy) have less toxicity. Early clinical results for patients with glioblastoma whose tumors had progressed during the standard temodar protocol have supported the generality of the results from experimental animal models (23). After tumor progression, a daily schedule of temodar at a dosage of 40 mg/square meter was used, which resulted in an additional median survival time of 11 months and a PFS-6 value of 50%, although it should be noted that only 12 patients were included in the study. The optimal dosage for this metronomic schedule of chemotherapy remains to be established because it now clear that dividing blood vessel cells are more sensitive to chemotherapy than are dividing tumor cells, but they are also much quicker to recover when chemotherapy is removed, which implies that any recess from using chemotherapy will allow the blood vessels feeding the tumor to quickly regrow.

Another example of this metronomic chemotherapy schedule with newly diagnosed glioblastoma patients (24) was reported in the past year. After completion of standard radiation treatment, continuous daily dosages of temozolomide approximately 1/10 of the typically used full dose were used in combination with vioxx (celebrex is now used instead). Median survival was 16 months and the authors of the report indicated that the protocol had minimal toxicity. The initial report of this study included only 13 patients, but a subsequent report after he number was expanded to 30 patients have yielded similar outcomes, with a median survival of 17 months..

The optimal use of metronomic chemotherapy schedules is most likely early in treatment before the tumor has evolved to produce many different growth factors. Results with the daily low-dose schedule of temozolomide were not as positive when administered to patients with recurrent tumors, with a PFS-6 value of only 19% (25). But interpretation of this study is problematic because patients were given a hiatus from chemotherapy after 7 weeks of treatment, and it is unclear from its survival functions whether the recurrences happened before or after the break from the daily schedule. A critical feature of the metronomic schedule approach is that the chemotherapy agent be constantly present until the tumor finally regresses from starvation, as regrowth of the blood vessels feeding the tumor can occur very rapidly.

It should be obvious that any number of different temodar schedules are possible, only a few of which have been investigated. One for which the early results seem especially promising (26) first presented one round of temodar at high dosage prior to radiation combined with daily low-dosage temodar during radiation and then the standard monthly high-dosage schedule thereafter. Median survival for 48 patients was 24 months, and 2-year survival was 57%. An interesting variation of this protocol would be to substitute the alternating week schedule for the monthly schedule after radiation was completed, which, based on the evidence reviewed above, should improve outcomes still further.

Combining the Standard Treatment with Additional Agents

A variety of data indicate that the efficacy of the standard treatment can be substantially improved by combining additional treatment agents with it. One example comes from a small phase II clinical trial that combined temodar with thalidomide, a known anti-angiogenic agent. Starting after the standard radiation treatment (27), patients received either thalidomide alone or thalidomide + temodar. The median survival time for the thalidomide-alone group was 63 weeks, while that for the group with thalidomide + temodar was 103 weeks. But the latter group involved only 25 patients, so it is obviously important to replicate these results.

A more recent study produced a more conservative estimate of the benefits of the temodar-thalidomide combination., In contrast to the median survival time of 103 weeks from the clinical trial just described, this second trial using the combination of temodar + thalidomide with newly diagnosed patients produced a median survival time of 73 weeks, which is only marginally better than the 61 weeks from the now standard treatment of temodar alone (28).. Two differences in their protocols are evident: (1) The latter study used temodar and thalidomide during radiation which was then continued after radiation was finished; the earlier study began the temodar and thalidomide only after the standard radiation treatment was completed. (2). The dosage of thalidomide was considerably less in the earlier study. This latter difference is interesting because clinical trials using thalidomide as a single agent seem to have produced better results with lower dosages of the drug. It is possible, but not proven, that the dose-effect curve for thalidomide is non-monotonic just as it appears to be for some other agents that have angiogenesis as their target. However, the most likely difference in the results for the two studies is that the earlier study included many patients who had re-operations for their tumors when they recurred, while there is no mention of re-operations in the latter study. In fact when the number of patients who were progression-free at one year is considered (a measure that is not affected by any role of re-operation), the two studies have essentially identical results (28-29%) In any event, both studies show an improvement over the results with the standard treatment protocol. A subsequent study also failed to find a substantial improvement in outcome from adding thalidomide. (29) Newly diagnosed glioblastoma patients received temodar alone on the standard schedule or the combination of temodar and thalidomide. Median survival was 12 months for temodar alone and 13 months for the combination. When the combination of temodar + tthalidomide has been used with patients with recurrent GBM, (30) PFS-6 was 24%. Note, however, that this study used the maximum tolerated dose of thalidomide.

Several other nontraditional treatment agents have also been combined with temodar. When temodar has been combined with accutane, a retinoid used for acne treatment (also known as 13-cis-retinoic acid, to be discussed later), the PFS-6 improved from the 21% historical value of temodar alone to 32% (31) When combined with a new drug called marimastat (32), PFS-6 was 39%. Marimastat is one of the new cytostatic drugs which stops tumor growth by inhibiting the enzyme process whereby the tumor digests the extracellular matrix of surrounding cells, allowing the tumor to invade the adjacent tissue. But marimastat has the unfortunate side effect of severe arthralgia and also is not available outside of clinical trials. Temozolomide has also been combined with interferon alfa-2b, which produced a PFS-6 value of 38% for glioblastoma patients (33).

Temodar has also been combined with several conventional chemotherapies. When combined with CPT-11, drug developed for colon cancer but now being intensively studied in its own right as a treatment for brain cancer, the PFS-6 was 38-39% (34). The combination of temodar with BCNU, the traditional chemotherapy for glioblastomas has also being studied, but has been complicated by issues of toxicity and the optimal schedule of dose administration for the two drugs. However, a recent published report failed to show any benefit of combining BCNU with temodar, compared to temodar alone, as the PFS-6 for the combination was only 21 weeks, accompanied by considerable toxicity (35). But more favorable results come a study (36) that used the BCNU-temodar combination with patients with inoperable tumors, after diagnosis before the standard radiation. This patient population has an especially poor prognosis with a historical median survival of 5-9 months. The result of the combination was a median survival of 12.7 months. The authors of the study also noted that the toxicity caused by the combination depended critically on the sequence of the two drugs, as much less toxicity occurred when BCNU was presented first in the sequence. Perhaps the best results from this type of combination study has come from the combination of CCNU with temodar, on a schedule of CCNU on day 1, temodar on days 2-6 of every monthly cycle (37). Here the median survival time for 31 patients was 22.6 months while the 2-year survival rate was 45%. However these impressive survival rates (compared to temodar alone) was accompanied by considerable toxicity.

An improvement in results relative those obtained with temodar alone has also been reported when temodar has been combined with cisplatin, In a pair of clinical studies performed in Italy (38, 39) with patients with recurrent tumors), the PFS-6 was 34% and 35%. Temodar has also been combined with procarbazine (40). While the report of that study did not include the PFS-6 statistic, it did report an unusually high percentage of tumor regressions, suggesting that this combination might be effective.

A treatment protocol that has produced especially impressive results combined temodar with cisplatin and VP-16 (given through the carotid artery). Cisplatin and VP-16 were given after surgery and continued for three cycles spaced every 3 weeks apart, followed by the standard protocol of radiation plus low-dose temodar, and then high dose temodar on the schedule of days 1-5 of every month. Of 15 patients studied so far median survival is 25 months (41)

There are also several clinical trials underway combining temodar with a variety of new biological agents that hold promise of improving outcomes without increasing treatment toxicity. These include drugs that target the signaling pathways involved in cell division, and agents that inhibit the growth of new blood vessels. In the latter category is a trial conducted jointly by several hospitals in New York, which combined temodar with celebrex, the anti-inflammatory drug that is now widely used for arthritis (42). For the 46 patients in the study (37 with GBM), the PFS-6 was 35%. I will discuss several of these new agents in greater detail in later sections.

It is important to recognize the limitations of the PFS-6 measure of treatment efficacy. While it does provide a rough means of comparing different treatments, it says very little about whether the various treatment protocols improve overall survival. It is entirely possible that treatments with low PFS-6 values produce a greater percentage of long-term survivors than those with higher PFS-6 values. Nevertheless, one major conclusion allowed by the above comparisons is that combinations of treatments are often superior to single-agent treatments, and that the combinations can include agents of relatively mild toxicity (e.g.,accutane, celebrex). It is feasible that the use of such lower-toxicity agents will allow combinations involving 3 and 4 different agents, which presumably should improve treatment outcome still further.

In addition to thalidomide, celebrex and, accutane, a variety of other agents seem likely to improve treatment outcome, including prescription drugs developed for other purposes, and agents available without a prescription. Perhaps the most surprising agent that seems to add to treatment effectiveness is lycopene, the carotenoid found most abundantly in tomatoes and other red vegetables and fruits (e.g., watermelon). Lycopene has been studied as a treatment for prostate cancer, with surprising effectiveness. In a study (43) reported at the 2005 meeting of the American Society of Clinical Oncology (ASCO), brain cancer patients received standard radiation therapy in combination with taxol (which is believed to be a radiation sensitizer). Prior to radiation patients were randomized to receive 8 mg of lycopene daily or a placebo. Of those receiving lycopene 80% had tumor regressions in response to the treatment while only 44% of placebo patients had a response using the same clinical criteria. Median time to disease progression showed a corresponding difference: 39 weeks for those receiving lycopene but only 21weeks for those receiving the placebo. It should be noted that the lycopene dosage used in this study was substantially less than that commonly used in the treatment of prostate cancer.

Another nontoxic candidate for adding to standard therapy is the old stomach acid drug, cimetidine (trade name tagamet). While no clinical studies have yet been reported using it with brain cancer, very impressive results have been reported from its use with colon cancer (44), the rationale being that it decreases cell migration (and hence the spread of the tumor beyond the original site) by affecting the critical genes controlling cellular adhesion. Support for its use comes from a recent experimental study using mice with implanted glioblastoma tumors that received either temozolomide or temozolomide + cimetidine (45). Survival was substantially longer in the latter group.

A later section will discuss several other nonprescription items that appear likely to add to treatment success. These include melatonin, PSK (a mushroom extract used widely in Japan), fish oil, and the seed oil, gamma linolenic acid.

Because of the improved results described above when additional agents have been added to temodar for patients with recurrent tumors, there now have been some recent clinical trials in which additional agents have been added to the initial treatment of patients just after diagnosis. Unfortunately, these trials have produced more confusion than clarification about the utility of combination treatments because the outcomes of different clinical trials have varied considerably.

In contrast to the improvement in clinical outcome when accutane was combined with temodar in the setting of recurrent tumors (31), a clinical trial with newly diagnosed patients that combined temodar with accutane produced less impressive results. . One study (46) with 55 evaluable patients used both accutane and low-dosage temodar during radiation, followed by full-dose temodar + accutane, and produced a median survival time of only 57 weeks and a two-year survival of 20%, both below the survival rates from the large clinical trial with the same protocol that used temodar without accutane. However, a second smaller (33 patients, 29 of whom had a GBM diagnosis) retrospective clinical trial (47) produced a median survival greater than two years.

The somewhat conflicting data from the clinical trials just reviewed prevents any clear recommendations about which are the optimal treatment cocktails. More information about these additional agents, and the results from clinical trials in which they have been studied, will be presented in later sections.

Other Chemotherapy Agents

While temodar is now the drug of choice for the initial treatment of glioblastoma, the majority of patients will receive minimal benefit. Unlike a generation ago, it is now common for patients who have failed one chemotherapy to proceed to other chemotherapy drugs. These include the nitrosoureas, BCNU and CCNU (and ACNU in Europe and Japan), and also the platinum drugs, and irinotecan, a drug developed for colon cancer known also known as CPT-11.

While BCNU was the standard chemotherapy treatment for glioblastomas for decades, there never was definitive evidence of its efficacy. A recent study of patients with tumors recurrent after radiation treatment is typical of the evidence (48). Of forty patients receiving BCNU at the time of tumor recurrence after radiation, the PFS-6 value was 17%, accompanied by considerable hepatic and pulmonary toxicity. Even less promising results were produced in a small Australian study in which BCNU was given to patients who had progressed when using temozolomide. Here 23 of 24 patients failed during the first six months (49).

Given that BCNU and PCV (which contains CCNU, an oral cousin of BCNU) have never been shown to be differentially effective, a somewhat surprising result has been reported using PCV for tumors recurrent after radiation (and for some patients after radiation and prior chemotherapy). In a relatively large study of 86 patients (50), PFS-6 was 38%, a value superior to that obtained for temodar in a comparable setting, although with considerable toxicity. However, another study (51) that used PCV for patients with recurrent tumors after temodar had failed had a PFS-6 value of only 13%. One plausible explanation for the discrepancy between the two studies is the nature of the prior treatment that had failed.

An important variation in the use of BCNU as the chemotherapy agent has been the development of polymer wafers known as gliadel. A number of such wafers are implanted throughout the tumor site at the time of surgery. The BCNU then gradually diffuses from the wafers into the surrounding brain. A possible problem with the treatment is that the drug will diffuse only a small distance from the implant sites, so that significant portions of the tumor will not make contact with the drug. A phase III clinical trial has demonstrated that survival time for recurrent GBM is significantly increased by the gliadel wafers relative to control subjects receiving wafers without BCNU, although the increase in survival time, while statistically significant, was relatively modest (52). The median survival time from the time of re-operation for the recurrent tumor was 31 weeks, while that for the placebo control group was 23 weeks. Survival rates six months after the treatment were 56% for the gliadel group while 36% for the placebo group. On the other hand, the differences in survival between the two groups was near zero when measured one year after treatment, indicating that the beneficial effects of gliadel were relatively short-term in nature. A second small randomized clinical trial was conducted in Europe, but involving patients who received gliadel at the time of initial surgery as a primary treatment, rather than as treatment for recurrent tumors (53). Here the survival rate after one year was 63% versus only 19% for those receiving the placebo. The two-year survival rate was 31% of the gliadel patients compared to only 6% for the placebo patients. However, both gliadel clinical trials involved patient populations that included approximately 1/3 of the patients with diagnoses other than glioblastomas, so the survival times that were obtained are inflated from what they would have been if only glioblastoma patients had been included. Probably the best estimate of the benefit of gliadel as an initial treatment comes from a. third much larger randomized clinical trial, also done in Europe (54), which reported a median survival of 13.9 months for patients receiving gliadel compared to a median survival of 11.6 months for patients implanted with placebo wafers. But again results have not yet been reported separately for glioblastomas vs. other high-grade gliomas. As with other forms of chemotherapy, however, larger differences are evident for long-term survival. After a follow-up period of 56 months, 9 of 120 patients who received gliadel were alive, compared to only 2 of 120 of those receiving the placebo.

Although gliadel avoids the systemic side effects of IV BCNU, which can be considerable, not only in terms of low blood counts but also in terms of a significant risk of major pulmonary problems, it produces its own side effects, including an elevated risk of intracranial infections and seizures (55). However, the lack of systemic toxicity makes gliadel a candidate for various drug combinations. A recent phase II trial with patients with recurrent tumors combined gliadel with 06 BG, the drug discussed above that depletes the enzyme involved in repair of chemotherapy-induced damage. Although only 24 patients have received the treatment at the time of the initial report of the results, the PFS-6 value was 68%, among the best yet reported (56). Similar promising results come from a recent small trial (16 patients) combining gliadel with carboplatin. A single dose of carboplatin was given 3-4 days after surgery during which gliadel wafers were implanted, and carboplatin was resumed after radiation was completed. Median survival was 22 months. (57) Impressive results have also been obtained with newly diagnosed patients who received the combination of radiation with low-dose temozolomide after the gliadel wafers were implanted at the time of initial surgery, followed by full-dose temozolomide after radiation was finished (58). While only 16 patients were enrolled in the study, the median survival time had not been reached at the time of the report of the study. One-year survival rate was 63%. A later report with more complete data indicated a median survival time of 19 months. The combination of gliadel with temodar during radiation also has been combined with a protocol that rotates among three different chemotherapy agents (temodar, CCNU, CPT-11) after radiation is completed. (59). Here the median survival was 90 weeks while median survival for patients receiving the same chemotherapy protocol without the gliadel wafers was 73 weeks.

A second class of chemotherapy that has been used for recurrent tumors are the platinum drugs, cisplatin and carboplatin. Carboplatin has increasingly become the preferred drug because it has significant less toxicity for eyes, ears and kidneys. In a representative study of carboplatin (60), 4 of 29 patients with recurrent glioma achieved partial tumor regressions, and another 10 achieved stable disease, for a response rate of 48%. Of those responding to carboplatin, the median time to tumor progression was 26 weeks. However, other treatment studies using the platinum drugs have produced highly variable results, with the source of the variability not clearly identifiable. One recent study of carboplatin has used intra-arterial infusion in combination with RMP-7 (Cereport), an agent that disrupts the blood-brain barrier. A clinical trial presented at the 1998 meeting of the American Society of Clinical Oncology reported a median survival time of 37 weeks for 37 patients with recurrent GBM (61.) However, a subsequent randomized clinical trial compared IV carboplatin with or without RMP-7 and found no advantage to adding RMP-7 (62).

More impressive results using cisplatin have come from its implantation directly into the tumor bed in polymer wafers similar to gliadel. A study in Belarus reported that patients receiving the cisplatin wafers at the time of initial surgery had a median survival time of 428 days, compared to 211 days for patients who received only radiation (63).

One of the newer chemotherapy agents is CPT-11 (also known as irinotecan), which has been FDA-approved for the treatment of colon cancer. Its application to gliomas has been pioneered by Dr. Henry Friedman at Duke University and is now undergoing clinical trials at a number of other medical centers as well. The initial results from the early trial were that 9 of 60 patients with recurrent gliomas had a confirmed partial response, while an additional 33 patients had stable disease lasting more than 12 weeks (64). However, results from other reported studies have been less positive (65, 66). Part of the reason for the discrepant outcomes may be that CPT-11 interacts pharmacologically with anti-seizure medications, causing its serum concentration to be decreased.

Like temodar , CPT-11 is now being studied in various combinations with other chemotherapy regimens, notably gliadel, intravenous BCNU, and temodar, although the results of these combinations are only now being reported. Some results are available for the combination of CPT-11 with BCNU, which produced a PFS-6 value of 30% for patients who had failed temozolomide-based initial chemotherapy (67). One interesting sidelight about CPT-11 is that the gastro-intestinal toxicity that it produces, which can be severe, is substantially attenuated by low dosages of thalidomide (see below for further discussion of thalidomide as a treatment agent in its own right). A recent study combining CPT-11 and thalidomide with patients who had failed both temodar and nitrosurea chemotherapy produced a PFS-6 value of 28%, so clearly the combination does have some activity (68).. Finally, CPT-11 has been combined with celebrex, with patients with recurrent tumors, and produced a PFS-6 value of 25% (69).

The major message of the clinical trials that have combined different chemotherapy agents together is that clinical outcomes are superior to single-agent treatments, although usually not dramatically so, and often with more toxicity. It has become increasingly evident that results at least as good as those from combining different chemotherapies can be obtained by combinations of chemotherapy with biological agents that lack the traditional toxicity profile of chemotherapy. Already mentioned (to be discussed further later) have been accutane, celebrex and thalidomide, but there now are a significant number of other new drugs, designed to target specific features of cellular growth, that offer the possibility of effective treatment cocktails.

New Treatment Agents Currently Available

In this next section, all of agents described are FDA-approved and thus can be obtained by prescription, despite the fact that their approvals have been for diseases other than brain tumors. This unfortunately causes some oncologists to be unwilling to prescribe them, although there is no legal basis for that reluctance. The drugs that will be described differ from conventional chemotherapy in that they do not kill all dividing cells, and as a result have little of the traditional toxicity for the bone marrow that causes weakening of the immune system and anemia. This makes them ideal candidates for drug cocktails, including combinations with chemotherapy. Several of these combinations appear sufficiently promising that they might be a better choice as the initial treatment after surgery than the temodar "gold standard". For example, patients whose MGMT gene is active are known to respond poorly to temodar, so that an alternative protocol could provide a better chance of treatment success.

Avastin (and related drugs)

Avastin (also known as Bevacizumab) is a monoclonal antibody that is the first drug explicitly designed to inhibit the growth of new blood vessels to receive FDA approval. It now is used for several different kinds of cancer, almost always in combination with one or another form of chemotherapy. Its first use with brain tumors was reported at a 2005 European neuro-oncology conference. (70). Avastin at a dose of 5 mg/kg was given every two weeks to 29 patients with recurrent tumors (apparently including both glioblastomas and grade III tumors), following by weekly infusions thereafter. Patients also received CPT-11 (irinotecan) concurrently with Avastin. Tumor regressions were evident after the first course of treatment, with 19 patients having either complete or partial regressions. Long-term survival data were not mature at the time of the report. It remains to be seen whether Avastin will have comparable effects in combination with chemotherapy drugs other than CPT-11. Avastin does increase the risk of intracranial bleeding, but in the aforementioned clinical trial, this occurred for only 1 of the 29 patients. Since the initial studies just described at least a dozen other studies have been reported, over ten of which at the 2007 meeting of ASCO. The largest of these, performed at Duke University (71), involved 68 patients with recurrent tumors, 35 of which had glioblastomas. For those the PFS-6 was 43% and median survival was 40 weeks. The latter number is disappointing given that a high percentage of patients had tumor regressions early in treatment. From the other reports a similar pattern emerged: a high response rate in terms of tumor regression, but then often a rapid regrowth of the tumor thereafter. Lacking from all of the studies is the percentage of patients who were long-term survivors (e.g., greater than 2 years). Sorely needed is further exploration of other agents that might be combined with avastin that would result in tumor responses of longer duration. Unfortunately, such combination studies have been inhibited by concerns that avastin increases both the risk of internal bleeding and blood clots.

There now are two other anti-angiogenic drugs that have received FDA approval, and several others undergoing clinical trials. The two already available are Sutent (also known as sunitinib) and Nexaver (also known as sorafenib). Both target several different signaling pathways whereas avastin targets only VEGF, the most potent signal produced by the tumor to recruit new blood vessel growth. (For further discussion of this issue see the later section on angiogenesis in the section on noteworthy clinical trials. Unfortunately, neither of these new drugs have published results for their application to gliomas. Three other new drugs still involved in clinical trials and currently without FDA approval, do have clinical results with glioblastoma, which will be discussed in the later section.

One interesting effect of avastin, and of other drugs that target VEGF, is that they reduce the edema common to brain tumors that is a major cause of the need for steroids. This is because VEGF causes a large number of small leaky capillaries which are pruned away when VEGF effects are blocked. Some have argued that the initial stage of blocking VEGF actually increases blood flow to the tumor, and hence makes it easier for chemotherapy agents to reach the tumor and be effective. This may be one reason that avastin produces such a high rate of early tumor regression.

STI-571 (Gleevec)

This small-molecule (also known as imatanib) treatment, which targets a specific gene involved in the growth of a form of leukemia, recently received a great deal of publicity because of its unprecedented effectiveness. As will be discussed later, this general strategy of identifying the growth signals for tumor growth and then targeting those signals, or their receptors, is one of the major new areas in cancer research. Such growth signaling channels often are involved in several different types of cancer. Although Gleevec was developed specifically for chronic myelogenous leukemia, the receptor involved has biochemical similarities to those for a more general type of growth signal, platelet-derived growth factor (PDGF), which is also involved in the growth of gliomas and other forms of cancer (e.g., small-cell lung cancer). Laboratory research has supported the importance of this similarity in that gleevec has been shown to strongly inhibit glioma growth, with the result that gleevec currently is being studied in clinical trials involving gliomas. Because it has approval for its usage for leukemia, the drug is also available outside of clinical trials. There now have been a number of studies reporting its use with high-grade gliomas. When used as a single agent it appears to have minimal activity, as one study reported a PFS-6 value of only 11%, accompanied by an increased risk of intracranial hemorrhaging (72), although another study, using different dosage levels, did report a number of tumor regressions, which they reported occurred very gradually over time (73). More promising results have been reported when gleevec is combined with hydroxyurea, an older drug that at one time was believed to be a radiation sensitizer among other functions. In the initial trial (74) with this combination, performed in Germany, 5 of 14 patients with recurrent glioblastomas had tumor regressions, another 5 had stable disease and 4 had disease progression. A more recent study (75) confirmed this activity and reported a PFS-6 value of 32%, with 4 of 30 patients alive without evidence of tumor progression over two years after the initiation of treatment. Yet another study, done in the USA, (76) produced a PFS-6 value of 27%. This level of efficacy is superior to that of temodar when used in the setting of recurrent tumors, although there has been no direct comparison of the different protocols for patients receiving their initial treatment after diagnosis It is possible that hydroxyurea is not the ideal chemotherapy agent to combine with gleevec. An alternative would be daily low-dose temodar, which has impressive efficacy in its own right as a single agent.

An interesting variation in the use of gleevec has been to begin its use for patients whose tumors have stabilized from prior treatment. Thirty patients whose tumors had been stable for 6 weeks received the gleevec –hydroxyurea combination (77), which produced a PFS-6 value of 60% and an 18-month overall survival rate of 53%.

A second variation in the use of gleevec was to restrict its usage for patients with recurrent tumors who tested positive for overexpression of the plate-derived growth factor receptor. (78) PDGFR is overexpressed in 50-65% of tumors, especially tumors labeled secondary glioblastomas, that are believed to have evolved from lower-grade tumors (in contrast to *de novo* glioblastomas that occur without such evolution). For this restricted patient population he PFS-6 value was 53%.

Given that avastin targets VEGF and gleevec targets PDGFR, the two most potent signals for angiogenesis, their combination might be expected to be synergistic or at least additive. Such combination has not occurred to my knowledge, in part because both drugs cause some degree of internal bleeding. However, a combination of gleevec with a different VEGF drug (PTK 787/ZK22584, tradename vatalanib) is now being studied in clinical trials, the phase I results of which was reported at the 2007 ASCO meeting (79). Although phase I trials are primarily concerned with establishing dosage levels, some efficacy is already apparent with this combination as 10 of 35 patients with recurrent glioblastomas have shown tumor regression and a number of others have shown stable disease.

Iressa, Tarceva, and Erbitux

These three recently FDA-approved drugs have the common feature that they target a growth-signaling channel known as the epidermal growth factor. Overexpression of EGF receptors is involved in the growth many different kinds of cancer, including more than half of glioblastomas. Iressa, (also called ZD 1839 and gefitinib) was the first of these drugs to be used with GBM (80); 53 patients with recurrent tumors received Iressa as a single agent, none of whom showed tumor regression. The 6-month PFS was only 13% and the median survival time was 39 weeks. There was no association between the degree of EGFR expression and clinical outcome. In a second study (81) 98 newly diagnosed GBM patients received Iressa as a single agent during and after radiation therapy. Here the median one-year survival rate was 54%, not obviously better than historical controls receiving radiation only. Again there was no relation between clinical outcome and the degree of EGFR expression.

A related drug, Tarceva (OSI-774 also known as erlotinib) has also being studied in clinical trials. A phase I trial (82) using it as a single agent for recurrent GBM patients failed to produce tumor regression for any patients and the PFS-6 value was zero. But two subsequent studies have produced substantially better results. A phase II study (83) with 48 patients with recurrent tumors produced complete or partial tumor regressions in four patients and 6-month PFS of 17%. A third study (84) produced tumor regressions of 50% or more in 6 of 30 patients ad a PFS-6 of 27%. Promising results have also come from a phase I trial combining Tarceva with temozolomide (85), which reported the results for 25 patients (6 partial responses, 2 minor responses, and 3 patients with stable disease. However, more disappointing results were reported when tarceva was added to the standard protocol for newly diagnosed patients of temodar + radiation (86). Given the variability in the results it is clear that much needs to be learned about when this class of drugs will or will not be effective. No clinical results using Erbitux for brain tumors as yet been reported.

An important development for understanding which patients respond to tarceva has come from a study (87) of 41 glioma patients (29 had GBMs) whose tumor pathologies were also assessed for their levels of a second protein called PKB/AKT, This is a signalling channel that results from inactivation of the PTEN gene, a tumor suppressor gene commonly mutated in glioblastomas. None of the tumors with high levels of PKB/AKT responded to treatment with Tarceva, whereas 8 of 18 tumors with low levels did respond to the treatment.

Because the inhibition of PKB/AKT should plausibly increase the effectiveness of EGFR inhibitors, a treatment strategy now being tested is the combination of EGFR inhibitors with rapamycin (trade name rapamune, generic name sirolimus), an existing drug used in organ transplants to suppress the immune system and prevent organ rejection, but which also inhibits the PKB/AKT signaling channel. A phase I trial (88) combined Iressa with rapamycin for 34 patients (25 GBM) with recurrent tumors; two patients had a partial tumor regression and 13 patients achieved stable disease. PFS-6 was 24%. A second clinical trial (89) with 28 heavily pretreated patients with low performance status (median

Karnofsky score of 60) received either Iressa or Tarceva in combination with rapamycin, with the result that 19% of patients had tumor regression while 50 % had stable disease, with a PFS-6 value of 25%.

It should be noted that several of the supplements to be discussed in a subsequent section have been shown to disrupt the epidermal growth factor signaling channel in various ways, as does accutane. Probably the most important is genistein, but quercetin and curcumin have this property as well.

One recent paper (90) of potential major importance has noted that tumors may not respond to treatments based on inhibition of the epidermal growth factor because of activation of the gene for a second growth factor known as the insulin-like growth factor I (IGF-I). IGF-I has also been implicated in the effect of tamoxifen. It is noteworthy, therefore, that one of the supplements to be discussed, silibinin,, is known to inhibit IGF-I (91). Lycopene also inhibits IGF-I. This suggests that silibinin and lycopene might substantially increase the effectiveness of any treatment that relies on EGFR inhibition.

A second possible reason for the ineffectiveness of the new drugs targeting the EGFR signaling channel is that the critical genetic marker for glioblastomas may not be the overexpression of the EGFR receptor, but rather a mutation of the normal receptor that produces activation of the receptor even in the absence of the growth signal. As a result, new drugs are under development that target this mutated receptor, including a vaccine that will be discussed in the section on Immunological Treatments.

Tamoxifen.

This drug is well known for its usage in the treatment of breast cancer. Its mode of action there is to compete with estrogen for attachment to the estrogen receptors of breast cells, thus reducing estrogen's ability to serve as a growth factor for carcinogenesis. This mode of action has little to do with tamoxifen's ability to serve as a therapeutic agent for gliomas. Effects on glioma are instead due to tamoxifen being an inhibitor of protein kinase C activity - an intracellular enzymatic reaction that is involved in glioma cell proliferation. Protein kinase C is now also known to play a significant role in stimulating angiogenesis. To obtain inhibition of PKC activity, and thus slow or stop the growth of the cancer cells, very high doses of tamoxifen are used, in contrast to its usage for breast cancer. The typical dosage for breast cancer is 10-20 mg daily, while for gliomas the dosage used has ranged from 160-240 mg per day. This high dosage is potentially problematic and does indeed have side effects. The most important is an increased risk of blood clots. For women, there is also an increase in the risk for uterine cancer, and for men, impotence and loss of libido are frequent problems. Weight gain is another significant side effect. Overall, however, such side effects are mild in comparison to traditional chemotherapy.

A stage II clinical trial (92, 93) evaluating the effects of tamoxifen for patients with recurrent gliomas has reported that it produced tumor regression in 25% of patients and stabilization of tumor growth for an additional 20% of patients. The percentage of patients with responses to treatment was greater with Grade III Astrocytomas than for patients with GBMs. The median survival time from the initiation of tamoxifen treatment was 16 months for Grade III tumors and 7.2 months for glioblastomas. This perhaps seems to be a minimal benefit (survival time for recurrent glioblastomas typically ranges from 3-8 months when second-line chemotherapy is used) but it should also be noted that a percentage of those who had either regression or stabilization had survival times greater than two years. Thus, for those "responders" tamoxifen produced a major benefit.

Tamoxifen has also been used in combination with traditional chemotherapy, because it should in principle reduce the level of chemo-resistance in addition to having its own direct effects on tumor growth. A European clinical trial combined tamoxifen with carboplatin as the initial treatment after radiation (94). Dosages of tamoxifen ranged from 40 to 120 mg/day, all of which were smaller than that used when tamoxifen has been used alone (160-240 mg/day). Combined over all dosages, the 12-month and 24-month survival rates were 52 and 32 %, respectively. For the patients receiving the highest dosage of tamoxifen, 12-month survival rate was 78%. In comparison, a matched set of subjects who received carboplatin alone after radiation had 12- and 24-month survival rates of 30% and 0%. However, a second similar study combining tamoxifen with carboplatin (95) reported a median survival time of only 55 weeks, which was only slightly superior to historical controls using carboplatin alone (48 weeks). However, the latter study noted that a minority of patients did have unusually long survival times, which was not reflected in the median survival times. The combination of carboplatin and temoxifen has also been studied with patients with recurrent tumors. Here the median survival time was 14 months, but only 6 months for the subset of 16 patients with GBM (96)

Tamoxifen with a dosage of 240 mg/day has also been studied in combination with BCNU as the initial treatment after radiation (97). Median survival time was 66.1 weeks, while the 1-year, 2-year, and 3-year survival rates 65%, 45% and 24%, respectively. It should be noted that while the 1-year survival rate and median survival time are only marginally greater than those obtained with BCNU alone, the 2-year and 3-year survival times are substantially greater. This benefit in terms of the number of longer-term survivors again reflects the fact that tamoxifen is effective only for a minority of patients, but for those its benefits can be very substantial. The fact that tamoxifen benefits only a minority of patients is relevant to the negative results of a phase III trial conducted in France (98). Patients received BCNU alone or BCNU in combination with 40-100 mg/day of tamoxifen (note that these dosages are substantially below that used in the other studies). No increase in median survival time was found, whereas the addition of tamoxifen did significantly increase the frequency of serious blood clots.

Most recent has been a trial combining tamoxifen with temodar (99). While details of this preliminary report are sketchy, its notable feature is that the combination treatment, presented as the initial treatment after standard radiation, resulted in all of the patients being alive at 12 months after diagnosis. More details are clearly needed, but the results as described are unusually promising. However, a second published trial combining temodar and tamoxifen (100) produced especially negative results and was in fact terminated early because of the low response rate and frequency of toxicity. This latter study is especially enigmatic because the schedule of temodar that was used was the daily low-dose schedule that was been reported recently to produce better results than alternative schedules of temodar. One important feature of tamoxifen is that its toxicity to glioma cells is due primarily to its first metabolite, which takes 2-8 weeks to reach asymptototic levels. Thus, short-term usage even with high dosages are not likely to be effective.

An important recent development with respect to tamoxifen has been the report (101) that it may be possible to predict which patients will be among the minority that benefits from tamoxifen. This Canadian study compared patients who responded to tamoxifen with those who did not and reported that there was a systematic difference in the metabolites from tamoxifen. This potentially allows a decision very early in treatment about whether tamoxifen is worth continuing. A second major development is that tamoxifen's efficacy may be increased by suppressing thyroid function (102). Thyroid hormones maintain the level of the insulin-like growth factor (IGF), which is now known to play an important role in causing resistance to several different kinds of cancer treatments (to be discussed further in a later section). Eleven of 22 patients with recurrent tumors became hypothyroid as a result of a drug treatment. Their median survival time was 10.1 months, versus 3.1 months for patients whose thyroid function was not effectively suppressed.

Accutane

This drug, which is FDA-approved for the treatment of severe acne, is an acid form of vitamin A chemically known as 13-cis-retinoic acid (also known as isotretinoin). Acid forms of Vitamin A are not stored in the liver; so unlike regular Vitamin A, high dosages may be used with much less risk of liver toxicity. Its presumed mechanisms of action are to activate genes that cause cancer cells to differentiate into normal cells and to block the receptor for the epidermal growth factor (EGFR). High levels of expression of that receptor cause cell division to occur at a rapid rate. A variety of other anti-proliferative effects have been identified as well.

A phase II clinical trial evaluating accutane for recurrent gliomas was conducted at the M. D. Anderson Brain Tumor Center (103). The median survival time was 58 weeks for glioblastoma patients and 34 weeks for grade III gliomas. This difference is survival time is opposite in direction than that obtained with other treatments. However, there was wide variability in both tumor types, so that the difference was not statistically reliable. Aggregated over all tumor types (43 evaluable patients) 3 achieved a partial tumor regression, 7 had minor regressions, and 13 had tumor stabilization, for a total response rate of approximately 50%. A recent more complete report of using accutane with 86 glioblastoma patients with recurrent tumors was less impressive. (104). Median survival time from the onset of treatment was 25 weeks and PFS-6 was 19%. Accutane now is used at M. D. Anderson as a "maintenance therapy" for patients after initial treatment with radiation or traditional chemotherapy. It also has been used in Germany for patients who have had a complete response to other treatment modalities as a maintenance therapy (105) The major side effects have been dry skin, cracked lips, and headaches, although occasional liver toxicity has also occurred. Increases in blood lipid levels frequently occur, often requiring anti- cholesterol medication such as Lipitor. Accutane also may produce severe birth defects if taken during pregnancy.

Because accutane's toxicity is very different from that of chemotherapy, it is now often used in combination with chemotherapy, notably temodar. When temodar is used alone for recurrent glioblastomas, the percentage of patients who have are alive without tumor progression six months after the start of treatment is 21%. When accutane is used in combination with temodar, the corresponding number is 32%. In the earlier section on drug combinations involving temodar, I discussed two recent studies that combined accutane with temodar in patients receiving their initial treatment. Unfortunately, the results from the two studies appear to be in conflict: the larger prospective study produced a median survival of only 57 weeks while the second, retrospective study produced a median survival greater than two years.

There is also experimental evidence that accutane is synergistic with other drugs that are known to cause cell differentiation (106). This approach to cancer treatment will be discussed more fully in a later section.

The similar pattern of treatment outcomes for tamoxifen and accutane raises an important question. Given that both seem to significantly benefit only a minority of patients, the issue is the overlap in the populations helped by the different treatments. That is, are patients helped by tamoxifen also be most likely to be helped by accutane, and vice-versa. If so, this suggests that the two agents should be synergistic in their effects, so that a patient receiving both agents should have a very high likelihood of a positive clinical outcome. If not, they should be additive, not necessarily in terms of benefit for individual patients, but instead in terms of the percentage of the total population who respond to one or the other treatment.

Thalidomide

This drug became infamous during the 1950s and 1960s because it produced a large number of birth defects involving abnormal or completely missing limbs. It is now believed that this was due to its effects on inhibiting new blood vessels because limb buds are especially dependent on the growth of new blood vessels for normal development. Thalidomide was initially approved by the FDA for the treatment of leprosy, but now also is approved for multiple myeloma. It also has several common off-label uses, especially melanoma, Kaposi's sarcoma, and prostate cancer. Unfortunately, a considerable amount of paperwork is necessary, both by the pharmacist who supplies it and the physician who prescribes it, so obtaining it for off-label uses is not as simple as having your physician write a prescription. These bureaucratic restrictions have been imposed despite the fact that the majority of potential users of the drug, males, and females past the age of menopause, are in no way affected by the drug's teratological potential.

Thalidomide's utility as a cancer treatment comes from it being the first anti-angiogenic drug that has been FDA approved, although it is now believed to have other mechanisms of action as well. In the first clinical trial using thalidomide as a single agent for the treatment of recurrent tumors (107), involving 36 patients with GBM or AA-III tumors, there were two partial regressions, two minor regressions, and 12 patients with stable disease for a minimum of 8 weeks. Median survival times were 74 weeks for those with tumor regression, 30 weeks for those with stable disease, and 22 weeks for those classified as nonresponders. However, PFS-6 was only 4%. The major side effects were somnolence (thalidomide was originally introduced for its sedative purposes; presumably such effects could be counteracted by various stimulants) neuropathy of various sorts, and constipation. Because such side effects are greater with higher dosages, it is of interest to note that results very comparable to the preceding study have been obtained in Australia using substantially lower dosages. Whereas the American studies have used a maximum dose of 1200 mg/day, the Australian study use a maximum dose of 500 mg/day (108).The best results using thalidomide as a single agent comes from a recently published study performed in Switzerland (27). Nineteen glioblastoma patients with glioblastomas received 200 mg/day of thalidomide, starting after radiation, escalating to 600 mg/day if tolerated. The actual median dose used was 200 mg/day. Median survival time was 63 weeks. Median progression-free survival was 17 weeks. Some patients had surgery for recurrent tumors so it is difficult to know how much of the survival time was due to the additional surgery.

The same study also reported the results of 25 patients who received the same regimen of thalidomide but in combination with temozolomide. Here the median survival time was 103 weeks and he median progression-free survival was 36 weeks.

Other trials have combined thalidomide with chemotherapy agents other than temozolomide. A clinical trial involving the combination of thalidomide with carboplatin for recurrent glioblastomas was reported at the 1999 meeting of the American Society for Clinical Oncology (109). Of 46 patients assessable for efficacy, 5 had a partial regression, 28 had stable disease and 13 had progressive disease. Estimated median survival for all patients was 40 weeks.

Thalidomide has also been studied in combination with BCNU (110) with patients with recurrent high-grade gliomas. Although the PFS-6 for all patients was only slightly better than temodar alone (27% vs. 21%), 9 of 40 patients had major tumor regressions while an additional 9 had stable disease. Both of these are higher than when temodar is used as a single agent in a similar population. Because of the disparity in the two different measures of treatment efficacy, any evaluation of the combination still remains unclear.

Comparison of the above results suggests an important point to highlight. Thalidomide appears to be more effective as a treatment when given as initial treatment rather than for tumors that have recurred. This appears to be true for anti-angiogenic treatment generally, the rationale being that mature tumors have a more developed vasculature so that preventing the growth of new blood vessels is less effective in starving the tumor.

Celebrex (and other NSAIDs)

Carcinogenesis of several types involves an inflammatory process. When anti-inflammatory drugs such as aspirin or ibuprofen are taken on a regular basis the incidence of colon cancer is reduced as much as 50%. This astonishing effectiveness has motivated investigation of the mechanisms of these benefits. One component of the inflammatory process is angiogenesis, which is now believed to be a critical component of cancer growth. COX-2 enzymes are believed to play an important role in inflammation, so that COX-2 inhibitors should reduce angiogenesis and inhibit tumor growth (111, 112). Many nonsteroidal anti-inflammatory drugs (NSAIDs) are known to be COX-2 inhibitors, but most (e.g., ibuprofen) also inhibit COX-1 enzymes, which are necessary for healthy maintenance of the stomach lining, which is why many users of NSAIDs eventually develop intolerance to them. Thus, much recent attention has been given to the new COX-2 inhibitors such as Celebrex and Vioxx, which were developed to avoid COX-1 inhibition for the purposes of arthritis treatment. Because inhibition of angiogenesis is one of the major new approaches to the treatment of cancer (see discussion in a later section) many oncologists have begun adding Celebrex or Vioxx to their regular treatment protocols, based on laboratory findings that Cox-2 inhibitors inhibit tumor growth. In the recent meetings of American Society for Clinical Oncology (ASCO), there were scores of new clinical trials reported that combined one or another Cox-2 inhibitor with conventional radiation, chemotherapy, and new targeted treatments. The great majority of these were phase 2 clinical trials which had only historical controls with the conventional treatment alone to assess the value of the added Cox-2 inhibitors, but almost all concluded there appeared to be a significant benefit, including two clinical trials using such a combination with glioblastomas.

The two clinical trials reported to date that have used celebrex in the treatment of gliomas combined it with temodar (42) or CPT-11 (69) and are described in the section on chemotherapy.

Because of the mild toxicity of NSAIDS, considerable recent research has investigated the mechanisms of its clinical benefit. Whereas initial research focused on the anti-angiogenic properties of this class of drugs, several other mechanisms have been identified, including the enhancement of various aspects of the immune system, and inhibition of the genes that prevent damaged cells from undergoing apoptosis. (113). Not all NSAIDS are equal in their anti-proliferative effects, as there is some evidence that one of them, celebrex, is considerably more potent than others in directly inhibiting tumor growth by down-regulating the cyclin proteins regulating the different stages of cell division (114). It is critical to note that many of the mechanisms by which NSAIDS work are strongly involved in the growth of high-grade gliomas, and that the expression of the cyclogenase enzyme that is the target of COX-2 inhibitors correlates strongly with the proliferation rate of glioblastoma tumors and correlates inversely with survival time (115, 116).

Chlorimipramine

This old FDA-approved drug was first used for the treatment of depression and now is used also for the treatment of obsessive-compulsive neuroses. Its rationale as a treatment for gliomas is that it selectively depresses mitochondrial function in glioma cells while leaving normal cells unaffected, causing the glioma cells to undergo apoptosis (programmed cell death. (117). Reported at the 2005 ASCO meeting (118) was a clinical trial evaluating the outcome of its use with 27 patients with high-grade gliomas (the distribution of GBMs vs. grade 3 tumors was not reported in the abstract, nor was the clinical history of the patients).Chlorimipramine was added to their treatment with doses from 25 mg daily escalated to 150 mg daily. Median survival was 27 months, with 20 of the 27 patients showed a partial tumor regressions.. This appears to be among the promising new treatments, although additional testing with more detailed reporting of the results is clearly needed before it can be recommended.

"Supplements" with Demonstrated Efficacy

Melatonin

This is a naturally occurring hormone secreted by the pineal gland that regulates the body's diurnal rhythm. It is commonly used for the treatment of jet lag and for insomnia. It is readily available in any health food store and most drug stores. Its role in cancer treatment has been predicated on the assumption that it boosts the immune system, with the current hypothesis being that it augments the activity of T-helper cells. It recently also has been shown to inhibit angiogenesis (119). It may also have direct cytotoxic effects on some types of cancer cells, notably melanoma cells. It has no known toxic side effects.

Clinical research on the use of melatonin for cancer treatment has been done primarily in Italy, where it has been used either as a single agent after radiation treatments, or in combination with various chemotherapy or immunotherapy regimens, most frequently interleukin-2. Part of the rationale for such combinations is that it decreases the side effects of the chemotherapy, especially with respect to blood counts. One of the clinical studies that has been reported (120) randomly assigned GBM patients either to radiation-alone or to radiation concomitant with 20 mg/day of melatonin. Melatonin was continued after completion of the radiation. Survival time was significantly longer for subjects receiving the melatonin. In terms of one-year survival rates, 6/14 patients receiving melatonin were alive, while only 1/16 patients without melatonin was alive.

This GBM study involved a relatively small number of patients, so that the effects should be considered tentative until a larger study is conducted. However, the effect of melatonin was statistically reliable even with the small number of subjects. Moreover, comparable effects have been reported in a similar design for the use of melatonin with advanced lung cancer (121). Like the GBM study, a substantial increase in survival rate occurred for the patients receiving melatonin.

To date there have been at least a dozen phase-2 clinical trials using melatonin either alone or in combination with other agents and five phase-3 trials involving random assignment of subjects to melatonin versus some type of control group. The majority of these have been relatively small and have involved patients in the terminal stages of their disease, which is perhaps why American oncologists have largely ignored them. However, several recent trials have been much larger and seem to leave little doubt that melatonin significantly increases the efficacy of chemotherapy. The most extensive randomized clinical trial involved 250 patients with advanced metastatic cancer of various types (122). Patients were randomly assigned to chemotherapy alone (using different chemotherapies for different types of cancer) or chemotherapy plus 20 mg of melatonin per day. Objective tumor regression occurred in 42 (including 6 complete regressions) of 124 patients receiving melatonin but in only 19/126 (with zero complete regressions) of the control patients. A comparable difference occurred for survival rate: 63/124 of those receiving melatonin were alive after one year while only 29/126 were alive of those receiving chemotherapy alone. A different trial, involving 100 patients with metastatic nonsmall-cell lung cancer (123), compared chemotherapy alone or chemotherapy in combination with melatonin. For the chemotherapy alone patients there were 9 of 51 who had a partial tumor regression, while 17 of the 49 chemo + melatonin patients had either a complete (2) or partial (15) regression. Twenty percent of the chemo-alone patients survived for one year and zero for two years, while the corresponding numbers for chemo + melatonin were 40% and 30%. Melatonin not only increased the efficacy of chemotherapy, but also significantly reduced its toxicity. These trials leave little doubt that the effects of melatonin are robust and of major clinical significance. Moreover, a recent study has shown that using multiple components of the pineal gland secretions instead of melatonin alone enhances clinical effectiveness still further (124).

PSK and other polysaccharides

PSK is the abbreviation for polysaccharide krestin (sometimes known simply as krestin), which is an extract from the mushroom, *Coriolus Versicolor.* It has become a standard component of cancer treatment protocols in Japan (a Chinese version of the same extract is known as PSP) for many different kinds of cancer, predicated on the assumption that it is an immune-system enhancer. Among the effects on the immune system that have been identified are gamma-interferon production, interleukin-2 production, and in increase in T-cell activity. Other effects include inhibition of matrix-degrading enzymes that underlie tumor invasion of adjacent tissue, and the inhibition of angiogenesis.

In one representative study, with non-small cell lung cancer (125), stage I patients receiving PSK (3 g/day) had a five-year survival rate of 39% compared to 22% for patients not receiving PSK. For stage III patients, the 5-year survival rate with PSK was 16% versus only 5% for those not receiving PSK. Both differences were statistically significant. Other studies involving colon cancer and stomach cancer have also shown that PSK substantially increased survival rates. I have found only one study that used PSK in the treatment of glioma, in combination with ACNU (a chemical cousin of

BCNU) and vincristine (126). The survival rate after one, two, and three years was 77%, 49%, and 47%, respectively. No control condition was studied that did not receive PSK, so exactly what its effect was is unclear. Note, however, that the two-year and three-year survival rates are substantially greater than that typically seen for GBM following traditional treatment with chemotherapy alone. However, the abstract of the study (the study was in an inaccessible Japanese journal) did not report the results separately for glioblastomas versus grade III gliomas.

PSK is not easily obtained in this country. The only source I have found is JHS Natural Products in Eugene, Oregon (phone # 541-344-1396 or 888-330-4691; website:www.jhsnp.com). A month's supply costs $125. Other mushroom extracts that also have the long-chain polysaccharides (beta-glucans) that appear to be the active ingredient in PSK are more readily available. These include maitake, reisha, and shitake mushrooms. However, none of these has the same level of scientific evidence for treatment efficacy in human clinical trials. Maitake D-fraction seems an especially promising mushroom extract based on a recent laboratory study of chemically-induced tumors in mice (127). Tumor growth was inhibited 90% when the mushroom extract was combined with chemotherapy versus an inhibition of only 50% when chemotherapy was used alone for control subjects.

Gamma-Linolenic Acid (GLA) and Fish Oil

GLA is an essential fatty acid found in evening primrose oil, borage seed oil, and black currant seed oil. At least 100 laboratory studies have shown it to be highly cytotoxic to many different kinds of cancer cells, with the presumed mechanism that metabolism of GLA by the cancer cells creates high levels of free radicals that are lethal to the cells. Iron and zinc potentiate this cytotoxic effect; Vitamin E (and perhaps other anti-oxidants) counteracts it. GLA is harmless to normal cells and has been shown to have clinical utility for a variety of disorders, notably rheumatoid arthritis and as a topical treatment for superficial bladder cancer. It also has been shown to lower LDL cholesterol and increase insulin sensitivity. GLA is also known to change the structure of cell membranes, which is believed to underlie the finding that it increases the effectiveness of both chemotherapy and radiation. At the same time GLA has been shown to protect normal cells from radiation damage.

Evidence that GLA is effective against gliomas comes from a study conducted in India (128, 129) in which GLA was infused directly into the tumor bed. Of the 15 patients treated, most had major tumor regressions, and 12 of the 15 were alive at the time of the report's publication (1-2 years later). The three who died were all quite elderly and probably would not have received any conventional treatment beyond radiation in this country. A subsequent study (130) involving patients with very advanced disease had notably less success but here too there were notable tumor regressions attributable to the treatment.

A critical question is whether oral ingestion of GLA has any clinical effects. A recent clinical trial involving its use for breast cancer substantiates that it does (131). Advanced breast cancer patients received the standard treatment of tamoxifen alone or tamoxifen in combination with GLA, in the form of 2.8 g of GLA/day. The source of GLA was borage seed oil, which is approximately 20-25% GLA, which meant that the patients were taking 12-15 g of borage seed oil per day. Borage seed oil is available in any health food store, usually in the form of 1000 mg capsules, although supposedly it can also be obtained in liquid oil form and makes tasty salad dressings. It is important to find a reliable source, because some sources have high alkaloid levels that are poisonous. The measure of treatment effectiveness in the breast cancer clinical trial was the status of patients three months after the initiation of treatment. With tamoxifen alone none of the patients had a complete response to treatment, 13% had partial regression of their tumors, while 81% had stable disease. For tamoxifen + GLA the corresponding percentages were 5, 37, and 55%, a significant improvement.

The use of GLA as a cancer treatment is controversial because one of its major metabolites is arachidonic acid, which is the precursor to both the lipoxygenase and cyclogenase inflammatory pathways. These inflammatory pathways are believed to stimulate the growth of cancer cells, which seems to contraindicate using GLA. However, it should be noted that GLA has been used successfully as a treatment for rheumatoid arthritis because of its anti-inflammatory effects, so obviously the story is more complicated. Part of the source of confusion is that the effects of GLA are dose-dependent. In laboratory studies low dosages have been shown to stimulate tumor growth, while at higher dosages the effect is clearly cytotoxic. (132, 133). A second important factor is the interaction with n-3 fatty acids (fish oil being the most common). When fish oil is also present, its metabolic pathway competes for enzymes that also are involved in GLA metabolism, thus preventing the formation of arachnidonic acid. The optimal use of GLA may therefore be in combination with fish oil, not as a single agent.

The major fatty acids found in fish oil, eicosapentenoic acid (EPA) and docosahexanoic acid (DHA), have also been demonstrated to have potent cytotoxic effects on cancer cells in numerous laboratory experiments. Part of their mechanism of action is similar to that of GLA, in that the metabolism of these fatty acids creates high levels of free radicals. In addition, a recent laboratory study has shown that EPA-treated tumors showed a significant arrest of cell division due to inhibition of cyclins at the G1 phase of cell division, which resulted in an increased rate of programmed cell death known as apoptosis (134).

A clinical trial comparing fish-oil supplements versus a placebo has also been reported, involving patients with several different types of advanced cancer (135). Thirty malnourished patients suffering from cachexia were randomly assigned to receive 18 g of fish oil per day in combination with 200 mg of Vitamin E, or a placebo sugar pill. An additional thirty subjects, adequately nourished, received a similar random assignment. For both groups the fish oil significantly increased survival. For the malnourished patients the median survival times, as estimated from their survivor functions, were 110 days for the patients receiving placebo and 210 days for patients in the fish oil group. For the adequately nourished patients, the corresponding numbers were 350 versus 500 days.

In laboratory studies (136) fish oil has also been shown to significantly increase the effectiveness of chemotherapy.

Vitamin D

Numerous laboratory studies have shown that Vitamin D is highly cytotoxic to cancer cells, due to several different mechanisms (although it is labeled a vitamin it more properly should be considered a hormone). While most research has focused on its ability to upregulate genes that cause cancer cells to differentiate into mature cells, other effects have also been identified, including cell cycle regulation, inhibition of the insulin-like growth factor, and the inhibition of angiogenesis (137). However the form of Vitamin D most commonly available is not readily usable for cancer treatments because the dosages producing anti-cancer effects also cause hypercalcemia, which can be life threatening (the major function of Vitamin D is to regulate calcium absorption and resorption from the bones and teeth). But like many vitamins/hormones, the generic designation refers not to a specific chemical structure but to a family of related molecules that may have different properties of various sorts. For Vitamin D several of these variants (commonly referred to as analogues) have been shown to effectively inhibit cancer cell growth but without the same degree of toxic hypercalcemia. In a recent paper in the Journal of Neuro-oncology (138), 10 patients with glioblastoma and one with grade III AA tumors received a form of Vitamin D called alfacalcidol in a dosage of .04 micrograms/kg each day, a dosage which produced no significant hypercalcemia. The median survival was 21 months, and three of the 11 were long-term survivors (greater than 5 years). Although the number of patients who responded to the treatment was not a high percentage , the fact that any relatively non-toxic treatment can produce that number of long-term survivors is remarkable. This is an especially interesting finding because there is strong reason to believe that Vitamin D is synergistic with retinoids such as accutane (139). Its effectiveness is also increased in the presence of dexamethesome (140) and a variety of anti-oxidants, notably carnosic acid, but also lycopene, curcumin, silibinin, and selenium (141).

Unfortunately, alfacalcidol is not available in the USA. But it is available in Europe and Canada. For those in the USA it is possible obtain it from various online marketers. One source that several members of the brain tumor community have used is Masters Marketing. Its web address is http://www.mastersmarketing.com. Undoubtedly there a number of other possible suppliers. It also should be noted that several other Vitamin D analogues are available, which also have much reduced hypercalcemic effects. One of these, paricalcitol, was developed for treatment of a disorder of the parathyroid gland, and recently has been the subject of several experimental studies (142, 143, 144) that have shown it to be highly cytotoxic to many different type of cancer. Given that other forms of Vitamin D have been shown to be highly cytotoxic to to glioblastoma cells, and that glioma cells are known to have receptors for Vitamin D, it seems likely that paricalcitol should have efficacy for glioblastoma as well. Unfortunately, its routine use is complicated by the fact it is available only in a form that requires intravenous injection.

The most common version of Vitamin D found in health food stores is cholecalciferol, which is the precursor of calcitriol, the form of Vitamin D utilized by the body. A recent study of cholecalciferol with prostate cancer patients who had progressed after standard therapy (145) suggests that this common form of Vitamin D may be clinically beneficial. Fifteen patients who had failed standard treatments were given 2000 I.U daily. PSA levels were reduced or stayed the same for 9 patients, and there was a reliable decrease in the rate of PSA increase for the remainder. No side effects of the treatment were reported by any of the patients.

It is important to note that all forms of Vitamin D can occasionally produce dangerous serum calcium levels, in part because there is a great deal of variability in their effects across individuals. It is thus important that blood calcium levels be monitored, especially while a nontoxic dosage is being established.

Supplements With Potential Efficacy But Not Yet Clinically Tested

Genistein

This is an isoflavone derived from soy products (it is also found in red clover extract) that has been shown in the laboratory to be highly cytotoxic to many different types of cancer, including glioma cells. In addition to the laboratory evidence, there is also substantial epidemiological evidence that high dietary intakes of soy products decrease cancer mortality by at approximately 50%. Only recently has it begun to be studied in clinical trials, mainly for prostate cancer, the results of which have been mixed.

Soy extracts containing genistein are available in most health-food stores. The concentration of genistein is often not well specified, so it is unclear what is actually in the extract. Most importantly, the listed amounts of genistein are so low that they are unlikely to provide much clinical benefit. The highest concentration (about 10 times greater than the others that I have found) is made by the Life Extension Foundation (phone: 800-841-5433; website: lef.org). It can be ordered from them or from L&H Vitamins, a discount mail-order company that is a good source for many types of products otherwise found in health-food stores (phone #: 800-221-1152).

Although there is as of yet no strong evidence of the clinical effectiveness of genistein, the laboratory studies that are available make a strong case for its potential efficacy. In one representative laboratory experiment mice received different concentrations of genistein added to their regular diet (146). The measure of its effect was the number of lung metastases caused by melanoma cells injected into the mice. The number of lung tumors was reduced by 50-75% depending upon the amount of genistein added to the diet. Interestingly, even greater inhibition of tumor growth was observed in another study when whole soy extracts were added to the diet, rather than genistein alone (soy contains numerous isoflavones other than genistein).

Recent experimental studies have examined the mechanisms whereby genistein produces its anti-cancer effects (147). The consensus is that this results from its ability to inhibit tyrosine kinase activity. This is a general class of chemical signals that strongly stimulate cell division. The epidermal growth factor, discussed earlier with respect to the mechanism of accutane's effect, is one member of this class of signals, and some investigators believe that genistein works by blocking the EGF receptor. Genistein also appears to produce inhibition of protein kinase C (discussed earlier with respect to the mechanisms of tamoxifen. This in turn suggests that a combination of genistein and tamoxifen might be especially effective. Finally there is increasing evidence that genistein is an inhibitor of angiogenesis.

Of special interest to brain cancer patients is a recent laboratory study in which glioblastomas cells were treated with a combination of genistein and BCNU (148). The result was a highly synergistic suppression of the rate of growth. This observation is important because genistein has much in common with new drugs being developed to block the EGF signaling channel, which themselves seem to be more effective when used in combination with conventional treatment modalities.

Selenium

This is a trace element commonly found in the soil, which is absorbed into various foods, most commonly onions and garlic. Its potency as an anti-cancer agent was discovered almost by accident in a randomized placebo-controlled trial in which selenium was being tested as a possible preventative agent for skin cancer (149). While selenium had no effect on the incidence of skin cancer, it had substantial effects on the incidence of other types of cancer, including lung, colorectal, prostate, and the total of all cancers. The most dramatic effect occurred for prostate cancer, for which the incidence was reduced by 63% for those receiving selenium relative to the rate in the placebo controls. The incidence of brain cancer was not recorded in this study. An important question is whether selenium is effective as a treatment for existing cancers in addition to being useful as a cancer preventative. Laboratory research suggests that it should indeed be effective, as it has been shown to inhibit tumor growth in a dose-dependent manner in vitro, and its use as a dietary supplement significantly inhibits the growth of pulmonary metastases after injection of melanoma cells into mice (150). Laboratory studies also have shown it to inhibit the growth of glioma cells (151). Recent studies have identified two of its mechanisms of action, inhibition of protein kinase C (152), known to be important in the growth of gliomas, and inhibition of angiogenesis (153). It is important to note that selenium can be highly toxic at high dosages, and that the degree of toxicity varies with the compound in which it comes. Selenomethionine is the preferred form because it is the least toxic. The most common dosage used is 200 micrograms/day, although dosages to 400-800 mcg/day have been used without evident toxicity. There is some evidence that its effects may be synergistic with Vitamin D.

Green Tea

Green tea has been consumed in both China and Japan for 5000 years based on its medicinal properties. It is now believed that its primary anti-cancer ingredients are polyphenolic catechins, the most prominent of which is epigallocatechin-3-galate (EGCG). A recent review has summarized its anti-cancer effects in several different animal models using both mice and rats (including major inhibition of glioblastoma cell lines), both when human tumors have been implanted and when they have been induced by various chemical carcinogens (154). In a representative study of chemically-induced tumors in mice (155), green tea was provided as the sole source of fluid, at a concentration of 6% (6 g of tea per liter of water), the incidence of lung tumors was reduced by 30%. The same study identified several different mechanisms of action, the most prominent of which was the inhibition of angiogenesis.

A recent review by the new Division of Alternative Medicine of the National Institutes of Health has identified green tea as the most promising of treatments advocated by proponents of alternative medicine. Accordingly, several clinical trials investigating its efficacy are ongoing. The only one reported to date used green tea in the treatment of patients with androgen independent metastatic prostate cancer (156). Dosage was 6 g of green tea per day. Only limited clinical benefit was reported. It is important to recognize that anti-angiogenic agents generally take a long time to produce clinical regressions, work better with less advanced stages of disease, and also work better in combination with other treatment agents.

Quercetin

This is a member of the class of flavonoids found in fruits and related plant products. Its most abundant sources are onions and apples. Like genistein it appears to be an inhibitor of tyrosine kinase activity, and appears to be synergistic with genistein when the two have been combined in laboratory studies involving both ovarian and breast cancer cell lines. It currently is being investigated in phase-1 clinical trials. Given that apples are one of its major sources, it is interesting that a story in *Nature* (June 22, 2000) has reported that material extracted from fresh apples inhibited in a dose-dependent manner the growth of both colon and liver cancer cell lines.

Curcumin

This is an ingredient in the Indian cooking spice, turmeric. It has been shown to inhibit the growth of cancer cells of various types in laboratory studies (157). Like genistein and quercetin, it inhibits the tyrosine kinase signaling and also inhibits angiogenesis. When the three supplements have been directly compared, curcumin was the more powerful inhibitor, but it also should be noted that its bioavailability from oral intake is limited. However, bioavailability supposedly is increased when curcumin is combined with piperine (the main ingredient in black pepper).

Silibinin (an ingredient of Silymarin)

Silymarin is an extract from the milk thistle plant that has been used extensively in Europe as an antidote for liver toxicity, due to mushroom poisoning and overdoses of tylenol. Its active ingredient is a molecule called silibinin. Recently a great deal of laboratory research has shown it to have anti-cancer effects as well. Like genistein and quercetin it is a tyrosine kinase inhibitor, but it appears to have multiple other effects, including the inhibition of the insulin-like growth factor (IGF) that contributes to the development of chemoresistance (158) (see the section on tamoxifen), and the inhibition of angiogenesis (159). It also inhibits the 5-lipoxygenase inflammatory pathway and suppresses nuclear factor kappa B, which is known to be antagonistic to apoptosis (160) It also appears to protect against common chemotherapy toxicities (161), while at the same time increasing the effectiveness of chemotherapy (162).

Lycopene

This is a carotenoid that is found most abundantly in tomatoes but occurs in various other red-colored vegetables as well (including watermelon). Unlike the most well-known carotenoid, beta-carotene, it does not get transformed into Vitamin A, and thus has no hepatic toxicity. In a small clinical trial involving prostate cancer patients about to undergo surgery (163), for those who consumed lycopene for several weeks before surgery both the size and malignancy of their tumors were significantly reduced relative to those not receiving lycopene. Several other more recent studies have shown that lycopene as a single agent reduces PSA in prostrate cancer patients whose tumors have become hormone-independent. In an experimental study involving both cell cultures and implanted glioma tumors in rats (164), lycopene (and beta-carotene) were found to substantially inhibit tumor growth in both experimental preparations, and in fact had a greater inhibitory effect than did a collection of retinoids commonly used clinically. As described in the earlier section on agents that can be combined with chemotherapy, a recent clinical trial (43) with glioma patients assessed the effect of adding 8 mg/day of lycopene to a protocol involving radiation + taxol . Eighty percent of patients receiving lycopene had either complete or partial tumor regressions, while this was true for only 44% of those receiving a placebo. Of further relevance to gliomas is that one of lycopene's mechanisms of action is to inhibit the insulin-like growth factor, which as noted above is involved in the development of resistance to a variety of different treatment agents. (165). Also of interest is evidence that it synergizes with Vitamin D (166).

Boswellic Acid

This an extract from Indian folk medicine used for its anti-inflammatory effects. Laboratory studies have shown that its mechanism of action is inhibition of the lipoxygenase inflammatory pathway, which is the source of inflammatory leukotrienes (167). This inflammatory pathway is distinct from the cyclogenase pathway that was discussed earlier in the section on *Celebrex and other NSAIDs*. Boswellic acid is now used in Germany as a substitute for steroids as a method of reducing the edema associated with gliomas. There have also been reports (168, 169) from in vivo animal laboratory experiments that it has direct anti-cancer effects . It seems plausible that its combination with celebrex or other COX-2 inhibitors might be synergistic.

Broccoli Sprouts

Brassica vegetables such as broccoli, cauliflower, brussel sprouts, and cabbage have long been believed to have anti-cancer properties, with the prevailing theory of the basis of that effect being that they contain a substance known as sulphoraphane. Recently it has been discovered that the 3-4 day-old sprouts of these vegetables contain 10-100 times the concentration of sulphoraphane as do the full-grown vegetables. To test whether the oral ingestion of sprouts has anti-cancer effects, dried broccoli sprouts were included in the diet of rats with chemically-induced cancers, with the result that considerable regression of the tumors were observed (170). Broccoli sprouts are also very tasty additions to salads.

Ellagic Acid

This is a phenolic compound present in fruits and nuts, including raspberries, blueberries, strawberries, and walnuts. In laboratory experiments it has been shown to potently inhibit the growth of various chemical-induced cancers, with the basis of the effect being an arrest of cell division in the G stage of cell division, thus producing the programmed cell death known as apoptosis. While there have been no trials to assess its clinical effects with human patients, it should be obvious that quantities of berries and nuts are among the more enjoyable dietary components, and even the possibility that they may have anti-cancer effects should encourage their usage.

Berberine

This is an alkaloid extract from *Coptides Rhizoma* commonly used in China as an herbal medicine. It is also found in high concentration in the widely-used supplement, goldenseal. In one laboratory study of using both various kinds of glioma cell cultures and implanted tumors in rodents (171), the cytotoxic effects of berberine were compared to those of BCNU and to the combination of berberine and BCNU. Berberine used alone produced a 91% kill rate in cell cultures, compared to 43% for BCNU. The combination produced a kill rate of 97%. Comparable results were obtained with the in vivo implanted tumors. Such results suggest that berberine is among the most promising treatment agents, but to date very little research using it has been reported.

Resveratrol

This is a naturally occurring polyphenol found most abundantly in grapes and mulberries. Red wine is among the sources. Numerous experimental studies have shown that it inhibits proliferation of various kinds of cancer, including leukemia, prostate, breast, and colon cancer. Among its mechanisms of action are activation of the P53 gene, inhibition of protein kinase C, and the inhibition of new blood vessel growth. In the one recent study of its use with implanted glioma tumors (172), rats received either sub-cutaneous injections or intra-cerebral injections of tumor cells, which in control animals rapidly grew and became fatal. With sub-cutaneous tumors a dose of resveratrol of 40mg/kg produced major growth inhibition with 70% of the rats becoming long-term survivors. A higher dosage (100 mg/kg) was necessary to inhibit the growth of the intracranial tumors, and even it was only marginally effective. The difference in outcome for the two preparations suggests that resveratrol may be impeded by the blood-brain barrier. However, the authors note that it had significant anti-angiogenic effects, which are not affected by the blood-brain barrier. Whether resveratrol has clinical utility for brain cancer is unclear, although it is known that anti-angiogenic agents of various sorts synergize with various kinds of conventional treatment.

Cannabis

After years of governmental discouragement of research on Cannabis (the plant from which marijuana is derived), the last few years has seen a proliferation of research on its mechanisms of action. One result of this research has been that cannabis inhibits the growth of various kinds of cancer cells, including gliomas (173). In the most recent paper (174), cannabinoids were shown to significantly inhibit angiogenesis in gliomas implanted in mice, which was accompanied by significant inhibition of glioma growth. The result is noteworthy because cannabis is among the more potent anti-nausea agents for controlling the side effects of chemotherapy. A recent small phase I trial infused pure THC (one of the active ingredients in cannabis) into the tumors of nine patients with recurrent tumors after surgery and radiation (and in some case chemotherapy), and produced a median survival time after treatment of 24 weeks (175). While this number is not impressive, it should be noted that this outcome is similar to that reported when temozolomide is used as a single agent for recurrent tumors. It should also be noted that the intracranial infusion of THC was probably not the ideal mode of drug delivery because of the limitations of all localized treatment procedures, and that THC itself is only one of several active components of cannibis. Systemic delivery of the whole set of molecules contained in cannabis seems likely to produce an improved outcome.

Skeptics of supplements/dietary components such as those discussed above have argued that the laboratory studies providing evidence for their anti-cancer effects have used dosages that can never be achieved in human patients, and therefore the supplements are unlikely to be useful clinically. Without a study of the dose-effect relations in clinical settings there is no easy way to evaluate this concern. However, in several cases investigators of the various substances have noted that their effects in the laboratory were obtained with dosages comparable to what easily can be realized by dietary supplementation, and in other cases there is direct clinical evidence supporting its use. In any event, for most of what has been discussed there is little if any risk to using the supplements, with the only cost being financial in nature. It is important to emphasize that cancer treatment of all types is probabilistic in its outcome. Thus, any agent that adds even a small amount to the probability that a treatment program will be successful, and which also has no toxicity, is something that should be taken seriously as an additional component of a multi-faceted treatment program.

Despite the significant evidence of treatment efficacy for at least some of the supplements that have been discussed, it is commonplace for oncologists to recommend strongly against the use of any kind of supplements to the standard treatment protocols. Part of the reason for this is simple ignorance of the evidence, but there is also the strongly held belief that many supplements have anti-oxidant properties (which is true), which may neutralize the cytotoxic effects of both radiation and chemotherapy due to the creation of free radicals. While the role of anti-oxidants in cancer treatment is too complex an issue to be discussed here, my own reading of the evidence is that there is no direct evidence for the anti-oxidants interfering wtth conventional treatment effects.

Perhaps the best example of evidence to the contrary is that the FDA has approved a drug named amifostine, which was designed to reduce the side effects of both radiation and chemotherapy (especially the platinum drugs). Amifostine is a very potent anti-oxidant, and several clinical trials were necessary to demonstrate that amifostine's benefits were not offset by reducing treatment efficacy. None of these trials indicated any reduction in treatment efficacy, and some indicated a small improvement. The fact that a skeptical FDA, based on the recommendations of its own advisory panels composed of oncologists, has approved amifostine is sufficient evidence to demonstrate that a blanket prohibition of supplements of all types is fundamentally mistaken, and based on a simplistic interpretation of a complex issue.

The Role of Radiation

For many years the only treatment (other then surgery) offered to patients with glioblastomas was radiation, based on the findings that radiation was the only treatment found to improve survival time beyond that of surgery alone in randomized clinical trials This continued to be the case in Europe until the last decade, but in this country chemotherapy (usually BCNU) gradually came to be accepted as a useful additional treatment component despite the absence of definitive evidence from clinical trials. Part of the reason for this acceptance of chemotherapy has been that very few patients receiving only radiation survive longer than two years (3-10%), compared to 20-25% of patients also receiving chemotherapy.

The initial approach to using radiation to treat gliomas was whole-head radiation, but this was abandoned because of the substantial neurological deficits that resulted, sometimes appearing a considerable time after treatment. Current clinical practice uses a more focused radiation field that includes only 2-3 cm beyond the periphery of the tumor site. Because of the potential for radiation necrosis, the currently accepted level of radiation that is considered safe is limited to 55-60 Gy. Even at this level, significant deficits may occur, often appearing several years after treatment. The most common causes of these deficits are damage to the myelin of the large white fibers, which are the main transmitters of information between different centers of the brain, and damage to the small blood vessels, which results in an inadequate blood supply to the brain and also increases the likelihood of strokes. An additional risk, not yet proven clinically because of the typical short survival times of glioblastoma patients, is the growth of secondary tumors due to the radiation damage to the DNA. However, experimental work with animal models has supported the reality of this risk (176). Three-year old normal rhesus normal monkeys were given whole brain radiation using a protocol similar to the common human radiation protocol and then followed for 2-9 years thereafter. A startling 82% of the monkeys developed glioblastoma tumors during that follow-up period. It is currently unclear to what degree a similar risk occurs for human patients who are long-term survivors.

The major additional use of radiation in the treatment of gliomas has been localized radiation to the tumor field, after the external-beam radiation treatment is finished (or sometimes concurrently), either by use of implanted radiation seeds (typically radioactive iodine), a procedure known as brachytherapy, the use of radiosurgery, or by the insertion into the tumor cavity of an inflatable balloon containing radioactive fluid (gliasite) .Previous editions of this treatment summary devoted considerable discussion to these treatments, but this now seems unwarranted. Two different randomized trials of brachytherapy failed to show any survival benefit even though the procedure causes considerable toxicity in terms of radiation necrosis (177). A recent randomized study of radiosurgery (178) similarly failed to show a benefit. Gliasite has yet to be studied in a randomized trial. The presumed reason that the initial studies indicated a survival benefit (usually increasing survival time about a year) was that the procedures were used only with a highly selected patient population, who otherwise had a good prognosis regardless of whether they received the procedure. This does not mean that the procedures are useless, as it is plausible, for example, that patients with small well- defined tumors could be successfully treated with radiosurgery. But given the toxicity associated with the procedures and the improvement in other treatment modalities, these additional forms of radiation are unlikely to be used much in the future.

A potentially important modification of the standard radiation protocols involves the use of hyperbaric oxygen prior to each radiation session. In a study conducted in Japan (179), high-grade glioma patients received the standard radiation protocol with the addition of hyperbaric oxygen 15 minutes prior to each radiation session. For the 31 glioblastoma patients, the median survival time was 17 months , with a very high rate of tumor regression. No data were available for 2-year survival. The use of hyperbaric oxygen was also reported to decrease the toxicity of radiation, although here to no long-term results were available

Radiation via Monoclonal Antibodies

An alternative for providing a radiation boost beyond that from the standard external field radiation involves attaching radioactive iodine-131 to a monoclonal antibody that targets a specific antigen, tenascin, which occurs on almost all high-grade glioma tumors. The monoclonal antibodies are infused directly into the tumor cavity over a period of several days, and reportedly produces much less radiation necrosis than either brachytherapy or radiosurgery. The median survival time from a phase 2 clinical trial of this treatment for recurrent GBM tumors was 56 weeks (180). In the first study that reported using this approach as initial treatment (181) patients received the monoclonal antibodies, followed by the standard external-beam radiation and then a year of chemotherapy. Of 33 patients, only one required re-operation for necrotic tissue caused by the radiation. Median survival time was 79 weeks for the patients with glioblastoma (27 of 33 of total patients) and 87 weeks for all patients. Estimated two-year survival rate for GBM patients was 35%. At the present time, however, only one treatment center (Duke University) uses this procedure, as it continues to be studied in clinical trials.

Noteworthy Clinical Trials

The treatments that have been discussed involve agents that have received FDA marketing approval, although often not for the treatment of brain cancer. This implies that the drugs are generally available, limited only by the willingness of oncologists to prescribe them "off-label". Many of the clinical trials that have been discussed have involved such off-label use, often in combinations with other drugs (e.g., temodar + thalidomide). No doubt future clinical trials will test a variety of other combinations, hopefully beyond simple two-way combinations. Unfortunately, it typically takes a long time from the initial demonstration of a promising new treatment to when it is accepted as a standard treatment. This is time that a patient with a glioblastoma tumor does not have. But there is no reason that an individual patient could not receive novel drug combinations outside of clinical trials, depending on the cooperation of a licensed physician (although insurance companies often will not pay for off-label drug use). At various points in the preceding discussion I described new combinations of drugs that have strong preliminary evidence of producing major improvements in clinical outcome (e.g., avastin +. CPT-11; the addition of chloroquine to chemotherapy), as well as modifications of standard protocols that similarly improve outcomes (e.g., the switch to the daily schedule or alternating week schedule of temozolomide). There is nothing in principle that prevents the combination of these potential improvements to produce a maximum benefit. There is of course always some risk of interactions producing unanticipated toxicities, but anyone with a glioblastoma diagnosis has a dire prognosis that requires moving beyond existing treatments that have been shown to be ineffective. Dying from one's tumor is an ugly reality that is by far the greater danger.

While an individual patient can do a great deal on his/her own to improve the chances of treatment success, many promising new treatment agents are not available outside of clinical trials, so that anyone wanting access to them must participate in such trials. The next section describes the major types of clinical trials that are now being conducted, some of which seem quite promising.

Anti-Angiogenesis

In order for tumors to grow they must recruit new blood vessels to meet the greatly increased energy demands. If the growth of new blood vessels could be prevented, the tumor's growth would necessarily stabilize or decrease, thus giving other treatments the opportunity to kill the cancerous cells. This approach has been increasingly supported by recent results. Thalidomide is the first anti-angiogenic drug used for brain cancer, although it has other mechanisms of action as well. Recently it has been joined by Avastin and Gleevec, both of which have produced some of the best results reported in clinical trials (see their separate discussion in previous sections). The even newer drugs Sutent and Nexaver, have not yet been studied with brain cancer, but it is likely that such clinical trials will be conducted in the near future. In addition, agents developed for other purposes, including celebrex, tamoxifen, and accutane, all have shown anti-angiogenic properties in experimental settings.

As promising as the recent results with these new agents have been, it is nevertheless important to appreciate the complexity of the angiogenic process. Numerous different growth factors are secreted by tumors to stimulate blood vessel growth. At least a dozen such factors have been identified, the most important being fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor (VEGF), which is generally regarded as the most important. The multiplicity of growth factors is important to note because it implies there are redundant processes involved in stimulating blood vessel growth, which in turn suggests that targeting individual growth factors alone is unlikely to be an optimal approach.. It may be necessary to combine several different treatment agents, each targeting a different signaling channel, for angiogenesis to be suppressed completely.

Because anti-angiogenesis drugs are considered one of the most promising new approaches to cancer treatment, literally dozens of drug companies are developing their own approach to this new treatment modality. Among these is an analog of thalidomide called CC-5103 (also known as revimid), which was engineered to have thalidomide's therapeutic effects without its side effects. In a phase I trial with recurrent high-grade gliomas (182), little toxicity was observed and several patients had stable disease, although the results were too early to evaluate meaningfully except for toxicity, which was minimal. A second drug, PTK787 (also known as vatalanib, which inhibits the VEGF signaling channel (which is also the target of avastin), has been studied as a single agent and in combination with temodar. Of 47 evaluable GBM patients receiving it as a single agent, there were 2 partial tumor regressions, and 31 with stable disease, along with clear evidence that blood vessel growth had been inhibited (183). When studied in combination with temodar (184), several partial tumor regressions and stabilizations of disease were observed, but it is too early to determine whether this is an improvement over temodar used as a single agent.

A third anti-angiogenic drug, currently being studied in early stage clinical trials at the National Cancer Institute, is LY31765 (also known as enzastaurin), which targets a variant of protein kinase C that has been shown to be a critical part of the signaling pathway for VEGF. Of 92 patients reported on at the 2005 meeting of ASCO (185), tumor regressions have been seen in 22% of GBM patients and 25% of patients with anaplastic astrocytomas. and stable disease in a significant number of others. In addition, the treatment seems to have minimal toxicity. Because of the early promising results, enzastarin was advanced quickly into a phase III randomized trial, the details and results of which have not been published, although I have heard through the grapevine that the trial unfortunately failed to reach its planned criterion of efficacy.

Still another new anti-angiogenic drug under development is celingitide, which disrupts the molecular processes that allow individual cells to be joined to form a coherent blood vessel. In an early-stage clinical trial (186) involving 51 patients (37 with GBM) celingitide as a single agent produced 2 complete tumor regressions, 3 partial regressions, and four disease stabilizations. A later trial using the drug with patients with recurrent glioblastomas produced a PFS-6 of 16% and a median survival from the onset of celingitide treatment of 10 months for patients receiving the higher of two dose levels (187). Currently underway is another clinical trial combining cilengitide with the standard temodar + radiaton protocol, but results are not yet available.

All of the agents just discussed,continue to be studied in clinical trials and will likely not be generally available for another 2-3 years. Several other new anti-angiogenic drugs are also being developed but have not yet been tested with brain cancer.

Given that brain tumor patients are unlikely to have access to these new treatments for some time to come, it is of interest to note that at least a half-dozen agents, already discussed in earlier contexts, possess significant degrees of anti-angiogenic activity. These include tamoxifen, accutane, gamma-linolenic acid, genistein, PSK, selenium, curcumin, silibinin and green tea. Vitamin D3 also has potent anti-angiogenic effects.

One class of existing drugs that have significant anti-angiogenic effects are members of the tetracycline antibiotic family, specifically minocycline and doxycycline (188). These drugs also inhibit metalloproteinases, which are enzymes that break down the cell matrix of the surrounding cells that allows cancer cells to invade that tissue (189).

The mechanisms underlying the anti-angiogenesis effects of each of these agents are often unknown and possibly very different. Nevertheless, it seems feasible that a combination of these different agents might produce inhibition perhaps sufficient to be effective in its right, but also to substantially increase the effectiveness of traditional treatments, and that of other anti-angiogenic agents. For example, one recent laboratory study showed that the combination of thalidomide and sulindac (an anti-inflammatory analgesic used for arthritis) produced substantially greater inhibition of new blood vessel growth than did either agent in isolation (190). A number of other studies have also shown synergistic effects from combinations of different anti-angiogenic drugs.

An example of implementing a cocktail treatment using the anti-angiogenic approach comes from a report in USA Today (July 25, 2002) of a dog afflicted with cancer in its chest cavity (the specific type was not specified). Its successful treatment regimen included celebrex, tamoxifen, and doxycycline. Another successful combination for a bear, reported in the same article, was celebrex, thalidomide, and doxycycline. . Such reports offer support for the cocktail approach.

Receptor/Antigen Targeting

The underlying rationale of this approach is that cancerous cells have proteins expressed on their surface that are not expressed on normal cells. Thus, by addressing this protein with some type of toxic payload the tumor cells can be killed with minimal damage to the normal tissues. The difficulty of this approach is that even though a number of antigens are highly expressed by all malignant glioma cells, none are unique to glioma cells, so inevitably some toxicity to normal cells will occur.

An example of this type of treatment approach has already been discussed in the section on radiation, involving monoclonal antibodies targeting tenascin, an antigen present on almost all high-grade gliomas, while carrying a radiation load. Median survival from the time of diagnosis was approximately 18 months. The therapy was was associated with hematologic and neurologic toxicity in 27% and 15% of patients, respectively.

A second variation of this approach involved the infusion of a modified diptheria toxin into the tumor site, attached to a chemical (transferrin-CRM) that selectively binds with tumor cells. The toxin is then incorporated into the tumor and kills it. The results of the phase I clinical trial (191) were that at least a 50% reduction in tumor volume occurred in 9 of 15 patients, including two complete remissions. However, those patients receiving higher dosages of the drug exhibited MRI evidence of significant damage to the small blood vessels, including thrombosis and hemorrhage. In a subsequent phase II trial (192), 35% of 34 evaluable patients with recurrent GBMs had significant tumor regressions, with 5 complete regressions and 7 partial regressions. Median survival time was 37 weeks, and the longest survival time was 3.1 years. Toxicity was mainly significant edema, which could be controlled by steroids.

Yet another version of the same approach involves interleukin-13, which is conjugated with pseudomonas endootoxin, a bacteria-produced toxin which has been shown to be lethal to glioma cells.. The most recent results of this approach were reported at the 2005 meeting of ASCO. Seventy-four patients with recurrent glioblastomas were included across the trials (although dosage varied), with a median survival time of 46 weeks with several complete responses.(193). Several types of neurotoxicity were observed, although none was sufficiently severe to require treatment termination. The report also emphasized the importance of the placement of the catheters, as post-hoc analysis showed that patients with optimally placed catheters had a median survival time of 70 weeks. Unfortunately, this promising treatment protocol was tested in a phase III clinical trial in which it was compared to gliadel, with the result that no difference occurred for the two treatments. (194).

The most recent variation of antigen targeting approach involves a molecule named TM-601, which is derived from scorpion venom and has a very high affinity for binding with brain tumor cells. This molecule was combined with a radioactive iodine compound and single dose was given to 18 patients with recurrent tumors. (195) There was minimal toxicity and five patients had either a tumor regression or a long-lasting stable disease. Presumably the outcome could be improved if multiple doses of the compound were presented.

As promising as these targeted treatments appear to be, they may be limited by their use of non-systemic modes of delivery directly into the brain. Such substances do not diffuse widely throughout the neuropil, so that portions of the tumor not immediately accessible from the site of infusion may not be contacted by the toxic agent. Thus, some portion of the cancer cells would remain, and given their geometric growth rate, soon would present major clinical problems. This problem of making contact with all of the tumor cells is inherent in any approach that uses intra-cranial infusion, including those involving monoclonal antibodies and gene therapy. It is of course possible that this problem can be mitigated by repeated presentations of the therapeutic procedure, or, as in the case of the

IL-13 trials, use of a low-pressure diffusion system that spreads the treatment agent over a wider area of the brain.

Immunological Approaches

Because cancer cells have a genetic structure different from normal cells they generate foreign proteins that in principle should be detected by the immune system and evoke the same type of immune reaction as any foreign virus or bacteria. This basic fact suggests that strengthening one's immune system might be an effective approach to cancer treatment. Such an approach has an immediate appeal because it is surely preferable to strengthen the immune system than to poison the entire body in the hope the cancer cells will be killed before the body is depleted of vital resources. However attractive this philosophy may be, translating it into an effective cancer treatment has proven to be extraordinarily difficult. Contrary to general belief, immunological treatments are not benign to implement. Interferon treatment has very definite aversive side-effects, as do cytokines such as interleukin-2 and tumor necrosis factor, because their modus operandi is essentially to create an inflammatory immune reaction not unlike a severe allergic reaction. When this inflammatory process is too severe, it can in fact be fatal.

One of the more successful examples of the use of cytokine-based immunological treatment was reported in *Cancer* in 1995 (196). Lymphocyte killer cells were created by mixing the white blood cells of individual patients with those of unrelated donors, then allowing them to incubate for several days. The mixture of unrelated blood cells creates "angry white cells" that generate a wide array of different inflammatory cytokines. These cells were then infused through an intracranial catheter into the tumor bed in combination with additional dosages of IL-2. Patents received this regimen for multiple cycles until disease progression. The results were a median survival time of 53 weeks for patents with recurrent glioblastoma, which compares favorably with the 3-7 month survival times when recurrent tumors are treated with additional chemotherapy. Moreover, 6 of 28 patients survived longer than two years. The authors also argued that the results might be yet more positive if the patients received their treatment as the first option rather than for recurrence, because most patients at the time of recurrence already had chemotherapy, which had failed but nevertheless significantly weakened the immune system. This implies that immunotherapy should be the first treatment to be used, while chemotherapy should be reserved until immunotherapy has been shown to be ineffective. However, it should be noted that little further development of this approach has occurred in the past ten years.

A related immunological treatment has utilized a technique that amplifies the T cells that are generated by the individual cancer patient in response to tumor cells. Glioblastoma tumor cells gathered during surgery were cultured in the presence of growth factors and then injected subcutaneously back into the patients. After development of an immune reaction the lymph nodes draining the location of the injection were resected to obtain lymphocytes attacking the tumor cells, and these were cultured with a staphylococcus toxin and a low dosage of interleukin-2. This generated a large number of activated T cells, which then were presented to the patient by intravenous infusion. The results were that two of ten patients had tumor regression, one of which still persisted up to the time of the report of the study (over 17 months). Of the eight patients with progressive disease, four were alive after over one year, suggesting the treatment had some beneficial effect even in the absence of tumor regression (197).

VACCINES

The holy grail of immunological approaches to cancer treatment is the development of effective vaccines. In principle this should be possible because of the differences in the protein structure of cancer cells and normal cells. There are, however, two general problems that must be overcome. The first is that different individuals have tumors with different collections of antigens (proteins), so that generic vaccines are unlikely to be effective; thus patient-specific vaccines are required. The second problem is that the immune system is not an efficient detector of the tumor's foreign antigens. In part this is due to the tumor secreting enzymes that in effect provide a protective cloak preventing such detection. The larger the tumor the stronger is its defense mechanisms to counteract immune-system detection. This is one reason that most vaccines work best when there is a minimum of tumor burden.

Methods to enhance the detection of tumor antigens are now the subject of intensive research, for various types of cancer. The most successful approach to date involves the use of dendritic cells derived from the bone marrow, which have been characterized as "professional antigen-presenting cells". Dendritic cells are co-cultured with cells from the patient's tumor, and stimulated with granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-4. (GM-CSF is the growth factor used to counteract the decrease in white-cell blood counts due to chemotherapy.) This growth factor causes the mixture of tumor and dendritic cells to be expanded as well. This mixture is then injected into the patient, evoking an increased reaction from the immune system. In a phase -I clinical trial (198) nine newly diagnosed high-grade glioma patients received three separate vaccination spaced two weeks apart. Robust infiltration of T cells was detected in tumor specimens, and median survival was 455 days (compared to 257 days for a control population). A subsequent report (199) involving 8 GBM patients produced a median survival time of 133 weeks, compared to a median survival of 30 weeks of a comparable set of patients receiving other treatment protocols. At two years 44% of patients were progression free, compared to only 11% of patients treated with the gold standarrd of temodar during radiation and thereafter. Most recently, a related research group reported that the use of temodar after the vaccination treatment improved outcomes relative to the vaccine alone (200). The authors of the study hypothesized that the improved outcome was due to the vaccine having primed the apoptotic machinery of the cancer cells, such that chemotherapy was then able to trigger the apoptotic pathway.

A very different approach to developing a treatment vaccine, which has the important property of being usable "off-the-shelf", without modification for individual patients, targets the epidermal growth factor receptor, variant III, which occurs in a high percentage of GBMs (but not all). One reason that EGFR inhibitors such as Iressa have not been more effective is that they target the normal EGFR receptor, not this mutated receptor, which in fact has no ligand for EGF itself. EGF variant iii is also rarely seen in anything other than GBM tumors. Patients received an initial set of 3 vaccinations at two-week intervals, then received the standard temodar plus radiation treatment, and monthly vaccines thereafter. Median time to tumor progression for 23 patients was 12.1 months, compared to a median time of 7.1 months for patients receiving the same treatment without vaccination. Median survival in the vaccinated patients had not been reached at the time of the report (201). A subsequent trial in which the vaccine was given only to patients who were screened in advance for the mutant receptor before admission into the clinical trial. Here the median survival was 29 months (press release from Celdex Pharmaceuticals, June, 2007), one of the best clinical outcomes thus far reported

An alternative type of vaccine treatment utilizes viruses. Newcastle disease is a lethal chicken disease, which is caused by a virus that apparently is innocuous to humans, causing only transitory mild flue-like symptoms. It was developed as a cancer treatment in Hungary but has largely been ignored in this country until only recently. A recent paper in the *Journal of Clinical Oncology* reported the first use of a modified Newcastle virus in a phase I trial with various types of advanced tumors (202). Some tumor regressions were observed, along with clear responses of the immune system to the tumor tissue. Another early stage trial (203), again with a modified vaccine derived from the Newcastle virus, was conducted in Germany. Eleven patients with glioblastomas received the vaccine after surgery and radiation and there were notable immune responses. However the median survival was 46 weeks, which is not notably different from the standard treatment. However, no toxicity was evident, which suggests that treatment with the Newcastle virus could easily be combined with other treatments.

A second clinical trial involving a different variation of the Newcastle virus has been conducted in Israel. (204) Eleven patients with recurrent tumors received different dosing schedules in a Phase I trial. Median survival was 37 weeks with minimal toxicity, and three patients lived longer than a year. However, all patients eventually died.

One reason for believing that the Newcastle virus might increase survival in brain cancer patients is that a phase II study of its use with stage III lymph-node positive melanoma reported remarkable success, with a 10-year survival rate greater than 60% (205). The developer of the treatment (who is now retired) also recently reported the case histories of five successfully treated glioblastoma patients using his version of the vaccine (206). Four of these were very young children, and thus atypical of the general GBM population. The report also did not include the number of GBM patients that were unsuccessfully treated. Nevertheless, there are strong reasons to believe that the treatment has considerable potential.

There are several variations of treatments based on the Newcastle virus, depending on how the vaccine is prepared. In a German study with 25 glioma patients (207), the patients' tumor cells were infected with the virus and then the infected cells were re-injected multiple times. Median survival was 92 weeks, compared to 44 weeks to a set of pair-matched controls. The 1-year and 2-year survival rate were 88% and 36% for the patients receiving the vaccine, compared to 40% and 4% for the control patients.

A second virus under investigation in Calgary, Canada is the reovirus, which is found commonly in the human intestines and respiratory system but is innocuous. However, it is apparently lethal to glioma cells, both in the laboratory and in rodents implanted with glioma tumors (208). Its mechanism of action is to co-opt the RAS oncogene pathway, which is activated only in cancer cells. No data from ongoing clinical trials have yet been reported.

Still a third virus is a modified form of the herpes virus. Initial trials used a retrovirus version, which has the limitation that only the cells that were infected directly by the infused virus were affected, as the virus did not spread beyond cells that were dividing at the time the virus was presented. Subsequent trials have used an adenovirus version, which infects both dividing and non-dividing cells. Because the herpes virus can be lethal to the brain if allowed to proliferate, soon after the virus infusion patients receive ganciclovar, an effective anti-herpes agent. In one study using this technique performed at Mt. Sinai Hospital in New York (209), median survival of 12 patients with recurrent GBM tumors was 59 weeks from the point of treatment, with 50% of the patients alive 12 months after the treatment.. The authors also reported the absence of toxicity from the treatment, which was a major concern due to significant brain damage when the procedure was tested with monkeys. Why the difference from the monkey study's results is unclear.

More recent research with the herpes virus has been focused on forms of the virus that have been engineered to retain the anti-cancer effects of the virus but without its property of producing neurological inflammation. The first use of this modified virus in a clinical trial was in Glasgow, Scotland. Nine patients with recurrent glioblastomas received the virus injected directly into the tumor. Four were alive at the time of the report of the study, 14-24 months after the treatment (210). A subsequent study using this approach, conducted in Finland, reported a median survival time of 62 weeks (for a combination of newly diagnosed and recurrent tumor patients) compared to 38 weeks for a comparable set of control patients. Finally, research is underway to produce a recombinant DNA version of the polio virus (211), based on findings that the wild version of the virus cures glioma tumors in monkeys. The aim is to find a version of the virus that will retain the ability to kill gliomas but without the paralysis effects that makes polio a feared disease. As yet no clinical trials with this approach have been reported.

The fact that immunological treatments have produced at least some degree of success is encouraging, and highlights the need to strengthen the patient's immune function as much as possible. The effects of melatonin and mushroom extracts such as PSK presumably are due to such strengthening, and therefore should be generally useful. But the most dramatic evidence for the importance of immune-system function comes from the investigation of POLY ICLC, a double-stranded RNA, which is assumed to work by causing the body to produce interferon, and also by de-activating an as yet unknown tumor suppresser mechanism of the immune system. Its initial results for AA-III tumors were truly exceptional: the initial clinical trial with POLY- ICLC (in combination with CCNU for about 1/2 of the patients) reported that all but one patient with AA-III tumors were alive with a median follow-up time of 54 months (212). It was less effective for glioblastomas, with a median survival time of 19 months (but note that this too is greater than the standard treatment). There were minimal side effects except for a mild fever early in treatment. However, a more recent multi-center clinical trial with AA-III tumors produced much less impressive results (213), as the initial cohort of patients had a PFS-6 value of only 23%. Note, however, that the latter study involved patients with recurrent tumors while that of the earlier study involved patients after initial diagnosis. Currently underway are additional clinical trials in which POLY ICLC is combined with temodar, and also in combination with the dendritic vaccine described above.

Other Miscellaneous Treatments

Differentiation/Apoptotic Agents

Cancer cells share much in common with fetal cells. Rather than having the specialized properties of mature tissue, they divide rapidly without maturing into the adult form for which they were intended. Differentiation into mature cells is under genetic control, so a major approach to treating cancer is to upregulate the genes that cause the maturation process to occur. Several agents have been identified that serve this differentiation function. Already discussed have been accutane (13-cis retinoic acid) and Vitamin D, but also included in this category are members of the category of aromatic fatty acids, such as phenylbutyrate and phenylacetate. Valproic acid, a commonanti-convulsant, also is included in this category. Closely related to the control of differentiation are tumor suppressor genes (p53 and p21 are the most well-known) that signal the cell to undergo programmed cell death (apoptosis) when abnormal functions are detected. There is now increasing reason to believe that many cancers, including glioblastomas, grow uncontrollably because the genes normally regulating differentiation and apoptosis are inactive due to various types of mutations.

One source of this de-activation is due to an enzyme named histone deacetylase., which causes these genes to be silenced, thereby neutralizing the body's protective mechanisms against genetic mutations. Currently in clinical trials are various drugs that inhibit this enzyme, based on the assumption that such inhibition will allow the gene function to be restored. The results of these trials are not sufficiently mature to be evaluated here, but early-stage reports have indicated that promising activity has been observed. It is therefore of interest that the well-known Burzynski anti-neoplaston treatment protocol has the restoration of normal function for tumor-suppressor genes as its modus operandi. Because Burzynski has generated enormous controversy. I devoted several pages of discussion of Burzynski''s treatment in my book, cited at the beginning of this article. Unlike the opinion of many neuro-oncologists, that discussion concluded that his treatment had merit, with the critical issue being how its results compared with conventional treatment protocols.

After years of conflict with the FDA, Burzynski now has approval to conduct clinical trials under FDA oversight. Part of the terms of this agreement is that he supplies detailed records of each of the patients receiving his treatment. Presumably this means that his other reports of his results are reliable. A recent review of those results is presented in an alternative medicine journal (214). Of 80 patients with recurrent glioblastoma tumors, 19% had tumor regressons of greater than 50%, 9% had minor regressions , and 2% had stable disease. Median survival time from the start of treatment was 9 months. A subsequent report (215) of the results from 22 patients had a PFS-6 value of 50%. One of the individual components of his antineoplaston package is phenylacetate, which is a common fatty acid that smells much like urine, from which it was originally derived. Phenylacetate has been shown to be a potent inhibitor of glioma growth in vitro (cell cultures), and has been studied as a single agent in a phase II clinical trial (216). Of forty patients with recurrent gliomas three had significant tumor regression, while another seven had stable diseases. In a second more recent clinical trial using a different dosing schedule (217) there were no objective tumor regressions, but the median survival time was nine months, which is above the norm for patients receiving treatment for recurrent tumors. While the overall response rate in both studies was low, it is important to recognize that phenylacetate is only one of the components of the Burzynski's treatment.

Perhaps more promising than phenylacetate is phenylbutyrate, which is a prodrug for phenylacetate (meaning that it metabolizes into phenylacetate). Laboratory studies have shown that it strongly inhibits the growth of glioma cells (218), and a recent clinical study has reported a complete regression of an anaplastic astrocytoma tumor, which previously had failed to respond to conventional chemotherapy (219). However, a later report by the same research group indicated that this was the only clinical response out of a substantial number of patients. Phenylbutyrate is especially interesting because in laboratory studies it has been shown to be synergistic in its effects with accutane (220), and with Vitamin D (221, 222).

A new drug explicitly designed to inhibit histone deacetylase is vorinostat. Its initial clinical trial with glioblastoma patients was reported at the 2007 ASCO meeting (223). Of 68 patients with recurrent disease 23% were progression free at six months. Because of is unique mechanism of action, vorinostat seems well suited for combinations with other drugs that have different mechanisms of action, although such combination trials have not yet been reported.

As noted above, a common anti-epilepitic drug, valproic acid, is also an inhibitor of histone acetylase. It also has the advantage of not inducing liver enzymes that reduce the concentration of chemotherapy agents in the serum, which does occur in many oher ani-epileptic drugs (in fact it slightly increases their concentration, so that the concern is that the standard dosages need to be monitored for toxicity) That its use rather than other anti-epileptic drugs might improve clinical outcome is supported by a clinical trial comparing enzyme-inducing anti-convulsants with valpoic acid. Median survival for the former was 11 months, while median surival for those receiving valproic acid was 14 months. (224) That a change in the anti-convulsant medication can significantly improve clinical outcome has gone unnoticed in the neuro-oncology community, despite their being a principled rationale for why this should be true.

AntiSense Treatment

Antisense molecules are artificially constructed genes that contain RNA that is the complement of the RNA that signals the production of the proteins involved in driving cancer growth. By combining with the signaling RNA, antisense molecules de-activate their growth stimulating effects. One gene that is the final common pathway for a number of common oncogenes is transforming growth factor beta-2. As described in a report presented at the 2007 ASCO meeting, a new drug named AP 12009, which is the antisense molecule of TGF-Beta-2 was presented via catheters into the brains of patients with recurrent glioblastomas.(225) Out of 95 patients, 28 received a low dose of the drug, 33 received a high dose, and 34 received standard chemotherapy. Survival rates at 18 months were 21%, 24%, and 18%, and not significantly different. However, the authors did note that several long-term survivors occurred in the two anti-sense groups.

A second similar trial restricted to patients with recurrent grade 3 gliomas (anaplastic astrocytomas) was also reported. (226) Median survival in the chemotherapy group was 21 months, while that for the low-dose AP12009 group had not been reached at the time of the report. Moreover, survival rate at that point was 42% for the chemotherapy group but 67% for the antisense group.

PhotoDynamic Therapy

When a molecule named haemetaporphyrin is absorbed by brain tumor cells, exposure to high-intensity laser light will kill the cells. A treatment based on this rationale has been developed in Australia but apparently has been ignored elsewhere. Early results with this approach were not impressive but the most recent report of clinical trial results with patients with newly-diagnosed high-grade gliomas indicate greater success. For patients with grade III tumors median survial was 77 months while that for glioblastoma patients was 14 months (227). More impressive were long-term survival rates, as 73% of grade

III patients survived longer than 3 years, as did 25% of glioblastoma patients. The treatment was reported to have minimal toxicity.

Electrical Field Therapy

A small biotech company in Israel has developed a device called Novo-TTF, which uses electrical fields to disrupt tumor growth by interfering with cell division of cancerous cells, causing them to die instead of proliferating. Healthy brain cells rarely divide and thus are unaffected. The treatment involves wearing a collection of electrodes for 18 hours/day, which allows the patient to live otherwise normally. Of ten patients with recurrent glioblasomas, the median time to progresson was 26 weeks, the PFS-6 was 50%, the one-year survival was 68%, and the median survival was 62 weeks, all substantially better than most prior treatments for recurrent tumors. (228) Moreover, 2 of 10 patients were progression free for more than two years.

Concluding Remarks

In past editions of this treatment summary I have confined myself to describing the evidence for the various available treatment options. However, with each passing year the range of options has expanded, so it is difficult for the newly diagnosed patient, or their families, to discern which is the best treatment plan to follow. So I now depart from the practice of previous years and offer by own opinions about how to proceed, based on what I would do today if I were a newly diagnosed patient. Keep in mind that I am not a physician with direct contact with patients and the valuable information that provides. On the other hand, my opinions are not constrained by the conventions of the medical system which often hamstring oncologists in considering the possible options.

My first piece of advice is to seek treatment at a major brain tumor center. Their surgical techniques are more likely to be state-of-the-art, which in turn means the patient will be more likely to receive a complete resection, now known to be a strong contributor to longer survival. Equally important is that major centers will be better equipped to retain tumor samples that will allow various tests of genetic markers that have important implications for which treatments are most likely to be successful for the individual patient. A culture of live tumor cells is also important for the development of some of the vaccines that were discussed above.

Three tests seem important at the present time, although others undoubtedly will emerge in the near future. The first is for the level of MGMT activity, which predicts whether the standard treatment protocol involving temodar will be successful. If a high level of activity is detected, the standard protocol seems not to work any better than radiation, so a different treatment protocol is advisable. The second test is for the presence of the epidermal growth factor variant III mutation. The vaccine under development that targets that specific mutation seems extremely promising, so anyone with that mutation should seriously consider using the vaccine as a first treatment option, assuming that it soon becomes generally available. Note that combining the vaccine with chemotherapy actually seems to improve outcome, contrary to the typical expectation that immunotherapy and chemotherapy treatments are incompatible.

If the mutation for EPGFR III is not present, a vaccine approach is still a possibility because the DC-VAX vaccine developed at UCLA and Cedars Sinai in Los Angeles also seems especially promising, especially now that multiple periodic vaccinations are permitted in the treatment protocol.

Yet a third test is for the presence of overexpressed platelet-derived growth factor (PDGF), which is the target of gleevec. If there is high MGMT activity,which predicts that temodar will be ineffective, gleevec is a reasonable alternative, in combination with one or another chemotherapy agent. But this protocol is much more effective if the PDGF overexpression is present.

Assuming that temodar is to be used (which it can be even with the vaccine treatments), it is important to maximize its effectiveness. The best results to date have come from a modification of the usual protocol in which a round of full-strength temodar is administered prior to the start of radiation with lower-dose temodar and full-strength temodar thereafter. In this moderate-size study (28) with 48 patients, 2-year survival rate was 57%. If the standard monthly schedule of temodar were replaced by the alternating-week or daily schedules discussed earlier, the results should be improved still further.

A further modification of the standard protocol that should substantially improve outcome is the addition of chloroquine, which doubled survival time when added to the old chemotherapy standard, BCNU. While it is not certain that a similar benefit will occur with temodar, it seems likely given that both drugs are alkylating agents.

There are numerous other relatively benign treatment agents that should also improve outcome, as reviewed in the earlier section. As a strong believer in the cocktail approach to treatment, my general rule is that any treatment that does not add significantly to toxicity should be considered as an additional facet of treatment. These include accutane (but probably not during radiation), celebrex (which should be used during radiation), low doses of thalidomide, and tamoxifen. In reality, such combinations will be very difficult to obtain as few neuro-oncologists will cooperate with this approach.

The above suggestions apply to the initial treatment protocol. It is unclear whether these same approaches will work for patients with tumor recurrence. At present the best option for patients with recurrent tumors seems to be avastin + CPT-11, although much work is needed to increase the durability of its benefits. It is possible that the addition of other treatment agents such as thalidomide or chloroquine might be helpful, but at present we have no meaningful information. Enrolling in clinical trials is another option, as numerous new promising treatments are under development, especially those that target angiogenesis.

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