Personalized medicine in neuro-oncology

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The latest catch phrase in cancer medicine is ‘personalized medicine’ denoting the potential to devise and prescribe therapies based on molecular and genetic information quasi-unique to the patient and the patient’s tumor as well as therapies developed using cell line or rodent tumor model screens of drug candidates [1–8]. The molecular–genetic approach has the potential of being far more informative than the high-throughput cell line and/or rodent tumor model approach for a number of reasons. While some information can be obtained from glioblastoma cell lines and/or rodent tumor models, the main flaw of the cell line approach is the reality that, aside from glioblastoma, lower grade glial tumors do not grow well in culture without genetic manipulation nor do they grow in rodents. Furthermore, monolayer culture is not always informative or predictive of *in situ* patient tumors so, at the least, 3D culture methods should be used. We are aware that some investigators are testing drug and drug combinations in rodent intracerebral

tumor models in an effort to personalize drug therapy for patients. Unfortunately, that approach will not work well in glial tumors as the ability of tumor cells to grow in culture and in animals is limited to glioblastoma lines and not reliable for low- and mid-grade glioma tumors.

The use of molecular–genetic information for the personalized approach to the treatment of primary CNS tumors is a valid long-term goal. Currently, we know a great deal about the molecular and genetic characteristics of infiltrative gliomas from studies over the past decades [3–17]. They have taught that we can better establish glioma phenotype and lineage [18–22] based on molecular phenotype compared with standard histopathology, which heretofore was the main approach to classifying gliomas along the lines of their predominate cell type (astrocytoma, oligodendroglioma, ependymoma) and grading their malignancy (WHO grades I–IV). Molecular classification has also helped to define patient subgroups that

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have better prognosis within a specific histology and grade, a correlation that appears to also parallel benefit from alkylating drug treatment and irradiation [19,23–26]. For instance, patients whose tumors have co-deletion of chromosome 1p and 19q respond better to irradiation with PCV than those are not co-deleted [27], but on the other hand this also closely follows the oligodendroglioma phenotype in the former case and astrocytoma phenotype in the latter case [20,28].

Based on what we know today and what drug therapies we have to treat our glioma patients, I would argue that the personalized approach for the treatment of glioma patients is only a limited goal today. Certainly, predicting those patients with a histological low- and mid-grade glioma who are destined to respond poorly to conventional irradiation and alkylating agent therapy because of molecular-genetic features can be important as it might drive clinicians to use more aggressive radiation therapy and cytotoxic chemotherapy. Additionally, knowing subgroups of glioma patients with high-grade gliomas that might respond in an above average manner to radiation and alkylating agent chemotherapy, compared with those that would respond in an average or below average manner, is helpful to patients who seek to understand how long they might live with the tumor and potentially their chances of long-term survival and possible cure.

Today's knowledge base reflects molecular-genetic differences among tumors from patients of differing age, tumors of different cell lineage and tumors predestined to become glioblastoma. Aside from this important knowledge, we have little information that allows us to select among therapies. The real problem is that all treatment-related information is a reflection of the conventional triad of surgical resection, irradiation and cytotoxic alkylating chemotherapy. Even the predictive situation of chromosome 1p and 19q co-deletion for oligodendrogliomas and IDH and ATRX mutations, and MGMT promoter methylation for astrocytoma reflect the capacity to respond and benefit from this therapeutic triad. In addition, there is EGFR amplification and mutation, PTEN mutation and loss of chromosome 10 and TP53 mutation [8]. One exception is vaccine therapy with rindopepimut that appears to be able to neutralize the impact of EGFRviii mutant in GBM patients [29]. There are also efforts afield to evaluate selective inhibitors of PI3K and IDH

mutants in patients with glioblastoma [30]. One could presume that if we had additional therapies that target specific intracellular pathways and receptor signaling, we might find additional and different molecular-genetic patterns that will change what we will consider personalized therapy in the future.

Currently, the only anticancer drugs available to treat infiltrative gliomas are alkylating drugs. The first drugs approved were chloroethylnitrosoureas (CENU) that easily crossed normal brain capillaries (blood-brain barrier) and crosslinked DNA. The first, CCNU (lomustine), was approved as a single agent for intracranial tumors in 1976 and marketed under the brand name CeeNu. BCNU (carmustine) was US FDA approved in 1977 for multiple brain tumors (including glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma and metastatic brain tumors) and marketed as BiCNU. Procarbazine, a monofunctional alkylating agent, was used to treat CNS tumors in the early 1970s as a single agent [31] and in combination with carmustine and lomustine [32,33], however, FDA approval was never sought by Roche. The most recent alkylating agent approved, Temodar (temozolomide, TMZ), was approved in 1999 for patients with grade 3 anaplastic astrocytoma in a single-arm response rate clinical trial [34]. In a randomized trial comparing radiation with TMZ versus radiation alone, radiation with TMZ produced a median survival advantage of 2.5 months (14.6 months for TMZ+RT versus 12.1 months for radiation alone) [35]. Subsequently, TMZ was approved for the treatment of patients with newly diagnosed GBM concomitantly with radiation followed by maintenance TMZ treatment. In recent years, TMZ became the most widely used alkylating agent for the treatment of CNS malignancies based on its efficacy and relatively mild toxicity profile.

Two nonalkylating drugs, bevacizumab (avastin) and afinitor (everolimus), were approved for limited applications in glioma patients. In 2009, Avastin (bevacizumab), a humanized antibody against VEGF protein, received accelerated approval for the treatment of patients with progressive GBM following prior therapy [36,37]. However, subsequent Phase III studies demonstrated no survival advantage when used in an adjuvant setting with temozolomide and radiation therapy [38], and recent results reported in abstract form from a Phase III study in recurrent

disease also demonstrated no survival benefit of bevacizumab added to CCNU versus CCNU alone. In 2010, Afinitor (everolimus) received accelerated approval for the treatment of subependymal giant cell astrocytoma (SEGA), a WHO grade I tumor, based on an open-label, single-arm response-rate clinical trial conducted in patients with SEGA associated with tuberous sclerosis that showed, at 6 months, that 32% (9/28) of patients had a $\geq 50\%$ reduction in their tumor volume [39].

The dearth of anticancer agents available today to treat CNS cancers is, I believe, the major limitation of our ability to treat patients in a personalized approach. It also leads to another problem in our approach for gliomas. If you know that a patient will do poorly and have a below average response to radiation and alkylating agent chemotherapy, should the patient be told that these therapies will not work and hence will not be given? What therapy should we offer our patients in its stead? If there is nothing and there are no new drugs today to fill that void, should we really withhold therapy? I cannot, and have found it easier to tell patients that they may have a below average response to therapy, and I might try a combination strategy that might help the odds.

As discussed previously, we do not have the drugs we need to treat our patients. I also believe that the neuro-oncology community does not fully address the reality that we do not have noncytotoxic drugs that are brain penetrant, target specific and will be target resident for sufficient time to insure antitumor activity [40]. The failure of the 'new' and 'targeted' drugs studied over the past 20 years are not surprising since these were, for the most part, 'hand me down' drugs from pharmaceutical companies that were previously studied or FDA approved in other cancers but which failed the criteria of brain penetrance, target specificity and long

residence time. Because of the dearth of target-directed drugs and their poor pharmacology features, it has been impossible to be certain of target inhibition or to adequately test rational drug combinations apart from whether a targeted drug worked with TMZ (which is unlikely to uncover new pharmacologically based drug combination strategies). In many cases, these were combinations of convenience.

To, effectively, personalize therapy for CNS cancer patients we will need new CNS-specific drugs to complement or replace the alkylating agents and irradiation we use today. To achieve this goal in the years to come will require an extraordinary effort from the pharmaceutical and biotech industries as well as greater financial incentives from the major regulatory agencies (FDA and EMA) to either expand orphan drug exclusivity or patent protection [41]. CNS cancers are less than 1.5% of cancer in the USA, so to attract the scientific, pharmaceutical and financial commitments needed to create the new drugs needed, it will certainly require financial incentives in the future. Otherwise, we will have to accept the reality that it might take decades or more to achieve parity of outcomes with other cancers.

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