

PHARMACOKINETIC INTERACTIONS WITH ANTIEPILEPTIC DRUGS: ALWAYS THE BAD ACTOR OR SIMPLY MISUNDERSTOOD?

Correlation of Enzyme-Inducing Anticonvulsant Use with Outcome of Patients with Glioblastoma. Jaeckle KA, Ballman K, Furth A, Buckner JC. *Neurology* 2009;73(15):1207–1213. **BACKGROUND:** Clinical trials involving patients with glioblastoma (GBM) distinguish cohorts who are treated with enzyme-inducing anticonvulsants (EIA). Such anticonvulsants induce hepatic P450 microsomal enzymes, which accelerate the metabolism of certain chemotherapy and molecular targeted agents. However, the resultant effect of such induction on patient outcome has received limited study. **METHODS:** We performed a correlative analysis of baseline EIA use with outcome, using a cross-sectional database of 620 patients with newly diagnosed GBM treated prospectively on North Central Cancer Treatment Group trials. **RESULTS:** At registration, 72% were receiving treatment with EIA; 2% were receiving non-EIAs, and the 26% were not receiving anticonvulsants (26%). Surprisingly, in the multivariable Cox model, overall survival (OS) and progression-free survival (PFS) showed a positive correlation with EIA use (hazard ratio [HR] = 0.75, $p = 0.0028$ and HR = 0.80, $p = 0.022$), even after adjustment for the known prognostic factors of age, performance status, extent of resection, steroid use, and baseline neurocognitive function. Specifically, the median OS was longer in EIA compared with non-EIA patients (12.3 vs 10.7 months, $p = 0.0002$). Similarly, PFS was longer in EIA patients (5.6 vs 4.8 months, $p = 0.003$). No differences in median OS or PFS were observed when comparing patients with or without a history of seizures at baseline. **CONCLUSIONS:** Paradoxically, enzyme-inducing anticonvulsant (EIA) use correlated with superior outcome of patients with glioblastoma. These results suggest that in comparative clinical trials testing agents metabolized by P450 microsomal enzymes, treatment arms may need stratification for the proportion of patients receiving EIA.

COMMENTARY

Malignant gliomas represent some of the most clinically challenging, and destructive cancers. Glioblastoma multiforme is one of the most common primary brain tumors. In the United States, about 18,000 patients are diagnosed with a malignant primary brain tumor each year, with glioblastoma multiforme representing over 50% of these (1,2).

Standard treatment for this tumor consists of cytoreductive surgery, followed by radiation. Despite advances in surgical technique and stereotactic approaches to radiation therapy, prognosis remains dismal. Median survival time is approximately 9–12 months, with only 3 to 10 percent of patients surviving 5 years. In an effort to improve survival, chemotherapy is often administered to patients as adjuvant treatment. Unlike experiences with other solid tumors, such as breast or colon, chemotherapy does not offer any potential for cure with glioblastoma multiforme, and improvement in outcome (i.e., survival) has been only modest, with partial response rates of only 20 to 40 percent, with older patients probably deriving the least benefit (1). Meta-analyses of a variety of adjuvant regimens have suggested an additional survival time of only 1–2 months (2). For any individual patient, the addition of adjuvant chemotherapy is likely to result in only about a 15% reduction in death at 2 years (3). Thus, at best, adjuvant chemotherapy can be expected to provide modest benefit to the individual

patient, and the decision to employ it clearly must take the issues of tolerability and quality of life into consideration.

The most commonly administered chemotherapeutic agents include temozolomide, carmustine, procarbazine, lomustine, and vincristine. The relative ineffectiveness of systemically administered chemotherapy is likely multifactorial: 1) The blood–brain barrier poses a significant obstacle to transvascular extravasation of the drug into tumor tissue compartments. 2) Activity of efflux pumps, such as P-glycoprotein, also work to transport a significant portion of extravasated drug back in the systemic circulation (4). 3) The pharmacokinetic interactions between various chemotherapeutic agents and enzyme-inducing antiepileptic drugs (EIAEDs) may reduce the overall systemic exposure of these agents, thereby limiting drug concentration at the tumor site (5,6).

Treatment with antiepileptic drugs (AEDs) is frequently required in patients with glioblastoma, as between 20 and 60 percent of these individuals will develop seizures (7,8). AED monotherapy is usually employed, at least initially, to control seizures. Not uncommonly, tumor progression or increase in cerebral edema might result in loss of seizure control and necessitate AED polytherapy (6). While treatment of seizures in this population is clearly warranted, the use of AED prophylaxis in brain tumor patients without documented seizures is far more controversial, because there is a lack of evidence supporting its efficacy.

The EIAEDs, such as phenytoin and carbamazepine, induce both hepatic and intestinal cytochrome P450 microsomal enzymes. Pharmacokinetic studies have demonstrated that

the metabolism of several chemotherapeutic agents is accelerated when given in combination with EIAEDs, leading to the logical conclusion that concomitant treatment with an EIAED might lead to worsened clinical outcome (9). Indeed, in one small retrospective analysis, a modest improvement in survival time was noted in glioblastoma patients treated with the chemotherapeutic drug 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) plus valproic acid (13.9 months) versus 10.8 months in the group receiving CCNU plus an EIAED (6). Whether these differences were due to decreased efficacy of the chemotherapeutic agent by the inducing AED or by way of increased efficacy of the chemotherapeutic agent caused by the enzyme inhibitory properties of valproic acid is unclear. In addition, it is tempting to speculate that valproic acid may have contributed to efficacy from histone deacetylase inhibition, which has been suggested to result in antineoplastic activity for several malignancies (10). Given the potential limitations of many of the older generation AEDs, it is reasonable to question whether these agents should be used in this patient population. Indeed, conventional wisdom would seem to be that these agents be avoided and that, despite limited clinical data, newer nonenzyme-inducing AEDs be considered instead (11,12).

Intriguingly, a recent retrospective analysis by Jaekle and colleagues has challenged this conventional wisdom. In this study, the relationship between overall survival, progression-free survival, and EIAED use was assessed in patients who were enrolled prospectively in three National Cancer Institute-sponsored trials, which were conducted between 1992 and 2002. Nitrosoureas were utilized in many of the prospective trials in this analysis. Based upon the known pharmacokinetic interactions, one therefore would have predicted a negative impact upon survival with EIAED coadministration. Surprisingly, coadministration of nitrosoureas and EIAEDs was associated with improvement in both overall and progression-free survival. Overall survival was in fact approximately 2 months longer in patients receiving EIAEDs.

Prior to this study, conventional wisdom suggested that EIAED use would, if anything, result in shorter survival rates. Certainly, an apparent beneficial effect on outcome would not have been anticipated. Nonetheless, what are we to make of these findings? When one sees data they cannot explain, typically, there are only two possibilities: the data are wrong or not enough is known to properly explain the effect.

Clearly, most patients in this retrospective analysis were treated in an era of widespread use of prophylactic EIAEDs and before the availability of the newer generation non-EIAEDs, with the majority of patients evaluated having been accrued prior to 2000. Unfortunately, the investigators did not provide information for either group regarding the specific AEDs used, the dosages administered, and/or the serum concentrations recorded, which clearly complicates any ability to make

an adequate comparison between these groups of patients. One is also left wondering whether there are potential confounders, such as seizure frequency and severity, between the groups. Interestingly however, some potential confounding patient characteristics, such as steroid use, age, and performance status, were assessed and seemed similar between patient groups.

Accepting these potential limitations, there remains the curious finding of a modest apparent benefit from EIAED use. Although one or more of the older EIAEDs could possess antitumor activity, evidence for this effect is lacking. Perhaps a simpler explanation lies with drug tolerability. As discussed, EIAEDs increase metabolism of many commonly used antineoplastic agents. For instance, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) is metabolized in part by cytochrome P450 isozymes. In rodents, enzyme inducers, such as phenobarbital, increase BCNU denitrosation. Substantial reductions (40–50%) in the area under the concentration-time curve have been reported for drugs such as vinca alkaloids, taxanes, camptothecin, and etoposide when used with EIAEDs. Given the restricted transport of many of the agents into the tissue compartments of a brain tumor, is it possible that reduced systemic exposure actually benefits patients by limiting treatment toxicity and/or the ability to deliver greater drug doses? In a phase I study of irinotecan among patients with recurrent glioblastoma, systemic clearance of this agent was significantly increased, as expected, in patients receiving EIAEDs compared to those not receiving these drugs. Interestingly, although no complete responses were seen, all four patients showing a partial response were in the group receiving an EIAED. There were no responders among those individuals not receiving an EIAED. Furthermore, the maximal tolerated dose was approximately three-fold greater in those patients receiving the inducer, with no apparent differences in drug toxicity noted between groups (13). Similarly, in a prospective trial of imatinib, Reardon and colleagues noted that use of an EIAED was in fact an independent predictor of longer progression-free survival, despite lower serum imatinib concentrations in these patients (14).

Ultimately, the precise mechanisms underlying the observations made by Jaekle et al. remain unclear. Whether concurrent administration of an EIAED actually confers a beneficial or protective effect is purely speculative. Nevertheless, these results should cause a reevaluation of the potential impact of AEDs on adjuvant chemotherapy in patients with brain tumor. While it is tempting and seems only logical to extrapolate well-known pharmacokinetic data to clinical outcomes, the data presented by Jaekle and colleagues are a reminder that pharmacokinetics is only a tool and not necessarily a clinical outcome. While many drug interactions may adversely impact treatment, they are only one possible factor governing clinical response.

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