OSU-03012 in the Treatment of Glioblastoma

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ABSTRACT
In an article presented in this issue of Molecular Pharmacology, Yacoub et al. (p. 589) examine the actions of 2-amino-N-[4-5-(2-phenanthrenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenylacetamide (OSU-03012) on both primary and glioblastoma cell lines. The authors found that OSU-03012 could induce tumor cell death by itself but also acted as a strong sensitizing agent to radiotherapy-induced cell death. Glioblastoma cells were also more sensitive to this compound than nontransformed astrocytes. Radiation-induced cell death was refractory to small interfering RNA-directed inhibition of PDK1 but not OSU-03012. These results indicate that OSU-03012, which has been thought to primarily mediate antitumor effects via the inhibition of PDK1, has actions independent of PDK1. Furthermore, the authors demonstrated that the effects of OSU-03012 were independent of ERB-B1-vIII and PTEN expression. These are important findings because they start to identify a new mechanism to sensitize glioblastoma cells and also suggest that OSU-03012 could be combined with existing inhibitors to further sensitize tumor cells. In glioblastoma cells, OSU-03012 seemed to induce apoptosis via endoplasmic reticulum stress-induced PERK-dependent signaling. OSU-03012–induced death of the glioblastoma was only weakly suppressed by the pan-caspase inhibitor, N-benzyloxycarbonyl-Val-Ala-Asp, suggesting that OSU-03012–induced cell death was largely caspase-independent. Overall, these are exciting results and suggest that new more effective treatment options may be obtainable for people suffering from these deadly tumors.

Glioblastomas are the most common tumor arising from the central nervous system. Approximately 74,000 glioblastomas are diagnosed worldwide each year (Reardon et al., 2006), and there are indications that the incidence of these types of tumors is increasing (Hess et al., 2004). Glioblastoma multiforme is a malignant neoplasm that accounts for approximately 55% of all gliomas (Halatsch et al., 2006). Glioblastoma multiforme tumors arise from astrocytes, usually occur in the cerebellum, are irregularly shaped, and contain focal areas of necrosis.

If the glioblastoma is resectable, surgery is typically performed. However, there is some question as to the benefits of the surgical approach (Behin et al., 2003). Radiotherapy after surgical removal of the tumor has been shown to have some benefit (Behin et al., 2003). For those tumors that are not resectable, radiotherapy is often used as the primary form of treatment (Behin et al., 2003). However, even with radiotherapy the prognosis of patients having certain gliomas can be quite poor (Desaknai et al., 2003). Despite all the advances that have been made in cancer treatment, the proportion of patients who die from glioblastoma multiforme, the most common glioblastoma (Ohgaki et al., 2004). Nearly 60% of people with this type of cancer die within 6 months (Ohgaki et al., 2004).

The combination of chemotherapy and radiotherapy does not seem to produce additive or synergistic effects in regards to the treatment of gliomas (Shapiro et al., 1989; Kortmann et al., 2003). Part of the overall difficulty in treating these tumors is that they can be very complex and different from one another. Glioblastoma multiforme can develop as the
first occurrence of cancer in the body or from gliomas of lower grade (Tso et al., 2006). In addition, approximately 25% of glioblastomas express the mutant epidermal growth factor receptor ERB-B1 vIII (Halatsch et al., 2006). Tumors from patients with glioblastoma may or may not express proteins such as p53 or p16 (Behin et al., 2003; Youcoub et al., 2006). Treatment alternatives that could preferentially target glioblastoma cells and would be effective against a variety of glioblastomas would potentially benefit patients suffering from this deadly disease. The report by Youcoub et al. (2006) suggests that OSU-03012 has this potential. With the discovery that many cellular signaling pathways can have a role in transformation and in the prevention of cell death, many efforts have been made to inhibit protein kinases within these pathways to prevent the growth of cancer cells or induce their demise. The components of the PI3K and ERK signaling pathways are especially attractive targets as they can mediate both proliferative and antiapoptotic responses (Franklin and McCubrey, 2000). A number of efforts are underway to examine the ability of both ERK and PI3K inhibitors to induce apoptosis of transformed cells (Lee and McCubrey, 2002). Probably the most successful approach to targeting cellular signaling pathways at this point in time has been with imatinib mesylate (Gleevec/ST1571) (O’Hare et al., 2006), which targets the Bcr-Abl kinase and has had good success in the treatment of leukemia caused by the Philadelphia chromosome, although some patients develop resistance to this treatment (O’Hare et al., 2006). The success of this treatment is due in part to the specificity of imatinib mesylate for tumor cells. Additional efforts are being put forth to determine whether inhibitors of the components of different signaling pathways can synergize with conventional treatments. There has also been success in this area of research in that both ERK and PI3K inhibitors will synergize with radiotherapy and chemotherapy to induce cell death (Lee et al., 2004; O’Hare et al., 2006).

OSU-03012 is a celecoxib derivative that reportedly inhibits PDK1 (Zhu et al., 2004), an important kinase in signaling via the antiapoptotic PI3K pathway. Because of this activity, there has been an interest in determining whether this compound would be effective in inducing apoptosis by itself or with other cancer treatments, similar to the approach that has been used with other inhibitors of cellular signaling pathways. OSU-03012 has been shown to be effective in inducing cell death in a variety of tumor types, such as pancreatic (Li et al., 2006), colon (Caron et al., 2005), breast (Kucab et al., 2005), and glioblastoma (Youcoub et al., 2006). In addition, this compound seems to be able to act in synergy with imatinib mesylate to induce tumor cell death in persons who have developed resistance to imatinib mesylate alone (Tseng et al., 2005).

It is a rational idea that OSU-03012 mediates these effects through the inhibition of PDK1 (Li et al., 2006). However, it is possible that OSU-03012 could also mediate additional antitumor effects independently of PDK1. Celecoxib, the parent compound of OSU-03012, has been shown to induce apoptosis via ER stress and the induction of C/EBP homologous transcription factor (CHOP) (Tsutsumi et al., 2006). Two recent abstracts from the American Association for Cancer Research meeting indicate that OSU-03012 can kill cells by multiple mechanisms; one of these abstracts showed a poor correlation between PDK1 inhibition and OSU-03012 lethality (Hsu et al., 2006; Porchia et al., 2006). In the prototypical ER stress pathways, PERK has been reported to modulate eIF2α phosphorylation and the subsequent expression of CHOP (Koumenis 2006). The article from Youcoub et al. (2006) is the first to describe the ability of OSU-03012 to induce tumor cell killing via an ER stress- and PERK-dependent pathway. In addition, at the low concentrations of OSU-03012 used, no detectable increases in the phosphorylation of eIF2α were observed, suggesting that PERK was mediating apoptotic activities by a mechanism independent of CHOP. Figure 1 depicts the novel mechanism of action of OSU-03012–induced cell death in glioblastoma cells. These novel results will begin the identification of additional targets that can be used for the treatment of glioblastoma. In addition, the results also indicate that screening of OSU-03012 derivatives on the basis of their ability to inhibit PDK1 may not be the best approach to find novel compounds that could also be effective in inducing apoptosis by itself or with other cancer treatments, similar to the approach that has been used with other inhibitors of cellular signaling pathways.

Fig. 1. Proposed pathway by which OSU-03012 leads to cellular apoptosis. OSU-03012 induces an ER stress response and the subsequent activation of PERK. PERK activation leads to the release of cathepsins from lysosomal compartments and the released cathepsins cleave Bid. Bid acts on the mitochondria, where it causes the release of apoptosis inducing factor.
used for cancer treatment, because OSU-03012 also induces cell death by a form of ER stress.

OSU-03012 triggers cell death independent of BIM, BAX, or BAK; caspase activation; ERB-B1-vIII; p53; p16; and phosphatase and tensin homolog deleted on chromosome 10 expression in glioblastoma cells. The data in Table 1 and Fig. 2A of the article by Yacoub et al. (2006) in this issue of Molecular Pharmacology demonstrate that OSU-03012 could induce apoptosis in a number of glioblastomas that demonstrate a large amount of heterogeneity from each other. This is a good characteristic for a drug to have considering how heterogeneous different glioblastomas can be. In addition, the effects of OSU-03012 were more pronounced on the transformed cell lines and the primary glioblastoma cells than they were on primary astrocytes, indicating some selectivity of the treatment for tumor cells. One of the most exciting aspects of this work is the ability of OSU-03012 to synergize not only with an existing therapy for glioblastomas (radiotherapy) but also, because of its novel mechanism of action, with inhibitors of the cellular signaling pathways (Fig. 2). Based on the separate mechanisms of action, it will be important to determine whether the combination of radiotherapy, OSU-03012, and a kinase inhibitor promotes glioblastoma cell death to an even greater extent.

In summary, glioblastoma is a very deadly cancer and successful treatment protocols are lacking. The identification of new treatments or identification of mechanisms to make existing treatments more successful is needed. The investigations of Yacoub et al. (2006) indicate that OSU-03012 may be a compound that has promise in doing so. The next step will be to complete successful in vivo studies both using the compound by itself and in conjunction with different therapies.

References


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