Nelfinavir potentiation of imatinib cytotoxicity in meningioma cells via survivin inhibition

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Although most meningiomas are treated surgically, it may not be possible to completely remove atypical, malignant, and surgically inaccessible meningiomas; in the majority of these cases there is tumor recurrence. The authors have already reported initial preclinical results on the efficacy of imatinib in the treatment of meningiomas; however, a recent Phase II trial of imatinib in patients with recurrent meningiomas did not demonstrate significant antitumor activity. To enhance the activity of imatinib, the authors investigated the use of a combination therapy with nelfinavir on primary meningioma cells and meningioma cell lines IOMM-Lee and CH157.

Cytotoxicity was measured using methylthiotetrazole and colony formation assays. In low-dose combination therapy with imatinib, nelfinavir potentiated the antiproliferative and anti–colony formation effects of imatinib. Primary meningioma cells responded better to combination therapy than to imatinib alone. Treatment induced a dose-dependent antiproliferative effect, decreased cell survival, and inhibited colony formation. Western blotting demonstrated decreased levels of survivin protein on combination therapy. Because meningiomas have very high levels of survivin protein, survivin inhibition by nelfinavir may represent a potential mechanism for the additive effect observed with imatinib. Moreover, an increase in the proapoptotic Bax/Bcl-2 protein ratio was demonstrated with the combination of imatinib and nelfinavir.

The authors propose that nelfinavir not only potentiates imatinib efficacy, it also abrogates resistance to imatinib by decreasing survivin protein levels in meningiomas. In an in vivo assay, this combination therapy was found to be more effective than imatinib alone. More preclinical work with in vivo models is needed to determine if this new combination therapy will translate into a viable future therapy for meningiomas. (DOI: 10.3171/FOC-07/10/E9)

Key Words • imatinib • meningioma • nelfinavir • survivin

Meningiomas are common intracranial tumors that account for almost 22% of all intracranial neoplasms. They are twice as common in women as in men and are mostly seen in patients in their sixth and seventh decades of life. Meningiomas arise from the meningothelial cells in the arachnoid villi of the meninges and are categorized as benign (≥ 90%), atypical/borderline (5%), and malignant (3–5%). Although mostly benign in nature, meningiomas commonly present as an enlarging mass that eventually leads to compression of neural structures, leading to seizures or other neurological deficits secondary to this compression.

Abbreviations used in this paper: DMEM = Dulbecco’s modified Eagle medium; DSMO = dimethyl sulfoxide; EMA = epithelial membrane antigen; FBS = fetal bovine serum; GFAP = glial fibrillary acidic protein; MMT = methylthiotetrazole; PBS = phosphate buffered saline; PDGF = platelet-derived growth factor; PDGFR = PDGF receptor; SE = standard error; TUNEL = terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling.

Most meningiomas are treated surgically and have a favorable prognosis. With gross-total tumor removal, the recurrence rate is 11 to 15%, which nearly doubles to 29% with incomplete resection. Meningiomas are sometimes difficult or impossible to resect completely due to their proximity to vital neural structures. Such cases of incomplete resection are associated with higher rates of recurrence. Radiotherapy is given to patients as an adjuvant therapy if the resection is incomplete. Additionally, atypical and malignant meningiomas have a tendency to recur despite complete resection.

Treatment options for recurrent meningiomas include repeated surgery or radiotherapy in the form of fractionated or stereotactic single-dose radiation. However, radiotherapy may also be associated with neurotoxicity secondary to damage to peritumoral normal brain tissue. There is no clear-cut efficacy associated with chemotherapy, although a number of chemotherapeutic agents such as RU-486, hydroxyurea, lovastatin, fenretinide, interferon-alpha, pegvisomant, and verotoxin have been tried in preclinical and clinical settings.

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Dysregulation of signal transduction pathways and resulting aberrant signaling plays an important role in the pathogenesis of meningiomas. One particular family of growth factors is PDGF, which is known to play an important role in tumor cell growth, proliferation, migration and angiogenesis. The PDGF family of genes encodes the following growth factors: PDGF-A, PDGF-B, PDGF-C, and PDGF-D. These molecules bind to the tyrosine kinase receptors PDGFR-α and PDGFR-β, leading to receptor dimerization and the activation of downstream signaling pathways implicated in neoplastic transformation. The expression of PDGF ligands and PDGFRs have been found to be elevated in a number of cancers such as gliomas, meningiomas, and renal cell carcinoma, among others.

Imatinib is a selective tyrosine kinase inhibitor that has been approved by the Food and Drug Administration for the treatment of chronic myelogenous leukemia; and gastrointestinal stromal tumors. Imatinib mesylate (Gleevec, Novartis Pharmaceuticals) is a small molecule adenosine triphosphate analog that competitively binds to and inhibits BCR-Ab1 tyrosine kinase. Imatinib is successfully being used as a targeted strategy for chronic myelogenous leukemia and has also recently been approved for use in gastrointestinal stromal tumors. In addition to BCR-Ab1, imatinib also inhibits tyrosine phosphorylation of PDGFR and c-kit. Imatinib has been found to be effective in inhibiting malignant gliomas in vitro and in an in vivo intracranial nude mouse model. Other cancer models studied for imatinib activity include pancreatic cancer, dermatofibrosarcoma protuberans, lung cancer, colorectal cancer, thyroid cancer, ovarian cancer, melanoma, prostate cancer, small cell lung cancer, and cholangiocarcinoma, among others. Earlier work indicates coexpression of PDGF ligands A and B, and PDGFR-β in meningiomas, where the beta receptor was found to be functional and led to increased meningioma cell division on its activation.

Nelfinavir belongs to a class of drugs known as protease inhibitors. These are small molecule inhibitors of viral aspartyl proteases. Patients with HIV who receive protease inhibitor therapy were found to have a decreased incidence of Kaposi sarcoma and lymphoma, which led to studies into the antitumor properties of this class of drugs. Over all, there are multiple reports of the efficacy of this class of drugs in various tumor models including melanoma, fibrosarcoma, multiple myeloma, breast cancer, and prostate cancer.

We performed initial preclinical studies demonstrating the effectiveness of imatinib in the treatment of meningiomas because of the high number of PDGFRs present on these tumors, imatinib’s ability to inhibit phosphorylation of PDGFR, and the generally well-tolerated oral availability of the drug. These results, however, were not validated in a clinical trial. Recently, we demonstrated that the protease inhibitor nelfinavir induces endoplasmic reticulum stress in malignant gliomas. Because such stress may reduce survivin levels, which are elevated in meningiomas (both benign and malignant), we investigated the efficacy of a combination therapy of nelfinavir and imatinib as a chemotherapeutic approach for meningiomas. This treatment in cultured primary meningioma cells, and in meningioma cell lines IOMM-Lee and CH157, resulted in growth inhibition, inhibition of colony formation, and downregulation of survivin and bax protein levels. The combination treatment also resulted in a decreased growth of IOMM-Lee subcutaneous tumors in a rodent meningioma model.

Materials and Methods

Imatinib mesylate was obtained in 100 mg Gleevec tablets (Novartis). The tablets were powdered and dissolved in DMSO at a stock concentration of 50 mM. Nelfinavir was obtained as 625 mg Viracept tablets (Pfizer). The tablets were powdered and dissolved in ethanol at a stock concentration of 50 mM.

All cells were cultured in DMEM (Gibco) supplemented with 10% vol/vol FBS (Omega Scientific, Inc.), 100 U/ml penicillin, and 0.1 mg/ml streptomycin (Gibco) in a humidified incubator at 37°C in a 5% CO₂ atmosphere.

Meningioma Primary Cultures

Freshly resected tissue, pathologically confirmed to be a meningioma, was washed three to four times with DMEM supplemented with 10% vol/vol FBS, 100 U/ml penicillin, and 0.1 mg/ml streptomycin. The tissue was then cut into small pieces, suspended in 10 ml of DMEM containing 10% FBS, transferred into a conical tube, and incubated at 37°C in a water bath for 15 minutes. The mixture was then centrifuged at 1200 rpm for 5 minutes, after which the cell pellet was resuspended in DMEM supplemented with 10% FBS and plated in 25 cm² flasks. The debris and nonadherent cells were removed and the cells were allowed to grow. The medium in the flasks was changed every 3 to 4 days until the cells reached confluency, at which time the cells were trypsinized and passaged. Only low passage cultures were used for our experiments. To confirm the identity of primary cultures histologically as meningioma cells and exclude the presence of astrocytes or smooth muscle cells, cytopreparations were prepared and stained for the expression of GFAP, EMA, S100 protein, and vimentin. Meningiomas are positive for EMA and negative for GFAP, S100, and vimentin.

Immunohistochemical Analysis

Cytopreparations were prepared from primary meningioma cultures and the IOMM-Lee meningioma cell line by centrifugation of cells onto glass slides and drying overnight. The next day, the cytopreparations were fixed in 10% acetone and dried for 15 minutes. Endogenous peroxidase activity was quenched using a 0.3% H₂O₂ solution in PBS for 10 minutes, after which the slides were washed three times with PBS and blocked for 1 hour with 5% fat-free milk. Primary antibodies diluted at 1:50 in 2% milk were applied overnight. The slides were then washed twice with PBS and incubated with the appropriate secondary antibody at 1:200 dilution for 1 hour, followed by 30-minute incubation with Vectastain ABC kit (Vector Laboratories). The 3-amino, 9-ethyl-carbazole (AEC, Sigma–Aldrich) substrate solution was used as a chromogen. The slides were counterstained with Mayer hematoxylin (Sigma–Aldrich).

Methylthioutrazole Assay

Primary meningioma cells were seeded at a density of
while IOMM-Lee or CH157 cells were seeded at 3000 cells per well in 96-well plates in DMEM containing 10% FBS. The cells were allowed to adhere overnight. Forty-eight hours posttreatment with varying doses of imatinib or nelfinavir, 20 μl of 5 mg/ml MTT (Sigma-Aldrich) solution was added to each well and the plates were incubated for 4 hours at 37°C in a 5% CO₂ atmosphere. The medium was then removed, and 150 μl of solubilizing agent (DMSO, Sigma-Aldrich) was added to each well. The plates were shaken gently for 30 minutes on a benchtop shaker and read at 570 nm on the Phelex enzyme-linked immunosorbent assay reader (Lab-Line Instruments). All experiments were performed in quadruplicate.

**Colony Formation Assay**

One hundred IOMM-Lee or CH157 cells were plated in six-well plates in 10% DMEM solution and allowed to adhere overnight. The cells were then treated with different concentrations of imatinib and nelfinavir for 48 hours, after which the drug was removed and fresh medium was added. The cells were allowed to grow over the next 10 days, after which the media was removed and the cell colonies were stained with methylene blue and counted. All experiments were performed in triplicate.

**Western Blot Analysis**

The cells were lysed in radioimmunoprecipitation buffer, and equal amounts of protein from each sample were subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis and Western blot analysis, as described. Antibodies to survivin, GRP78, Bax, and Bcl-2 were purchased from Santa Cruz Biotech and used according to the manufacturer’s recommendations. As secondary antibodies, we applied horseradish peroxidase–conjugated goat anti–mouse antibodies (Vector Laboratories). Image development was performed with the addition of enhanced chemiluminescent detection solution (Amersham Biosciences Corp.) and exposure to Hyperfilm (Amersham).

**Establishment of the Subcutaneous Animal Model**

All animal protocols were approved by the Institutional Animal Care and Use Committee of the University of Southern California, and all applicable policies were strictly observed during the course of this study. Four- to 6-week-old male athymic nu/nu mice (weight 20–30 g) were obtained from Harlan and kept in a pathogen-free environment. The subcutaneous tumors were established by implanting 10⁶ IOMM-Lee cells in the right flank of the animal. The animals were divided into four groups: a control group that received no treatment, a nelfinavir-treated group, an imatinib-treated group, and a group that received combination treatment with imatinib and nelfinavir. Both imatinib and nelfinavir were delivered orally. Imatinib was administered at a dose of 100 mg/kg/day, whereas nelfinavir was administered at 150 mg/kg/day. The tumors were measured biweekly using Vernier calipers, and the volume was calculated by the formula length × width² × 0.5. Standard error and probability values were calculated.

**Statistical Analysis**

The Student t-test was used to determine statistical significance. Probability values less than 0.05 were considered significant.

**Results**

**In Vitro Assays**

Cytopreparations were prepared from low passage primary cultures and immunostained for GFAP, EMA, S100 protein, and vimentin.
protein, and vimentin. The primary cultures stained positive for EMA and negative for GFAP, S100 protein, and vimentin (Fig. 1). This confirmed the identity of the primary cultures used in our experiments as meningioma cells.

Methylthiotetrazole assays were used to quantify the inhibitory effects of imatinib and nelfinavir in meningioma cell lines and primary cultures. Meningioma primary culture cells were seeded into a 96-well plate in 10% DMEM solution and treated with varying concentrations of imatinib and nelfinavir for 48 hours. The results demonstrate a dose-dependent decrease in proliferation, which is significant on combination treatment in primary meningioma cultures (Fig. 2A). Similarly, MTT assays were also performed for the IOMM-Lee and the CH157 human meningioma cell lines. The IOMM-Lee or CH157 (5000 cells/well) were plated in a 96-well plate in 10% DMEM solution and treated with varying concentrations of imatinib and nelfinavir for 48 hours. Combination treatments demonstrated a dose-dependent decrease in cellular proliferation in both of these cell lines (Fig. 2B–C).

Colony formation assays were used to assess the effects of imatinib and nelfinavir on the IOMM-Lee and the CH157 cell lines. One hundred cells were plated in six-well plates and treated with varying concentrations of imatinib

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and nelfinavir for 48 hours. The cells were then allowed to form colonies over a period of 10 days. The colony formation assay therefore reflects the long-term survival of tumor cells after treatment. The results indicate that combination imatinib and nelfinavir therapy leads to a dose-dependent decrease in the colony formation ability of the IOMM-Lee cell line (Fig. 3A and B).

Cells from the IOMM-Lee meningioma cell line were treated with 10^{-6}/H9262 doses of imatinib and nelfinavir alone or in combination for 48 hours; lysates were subsequently prepared and subjected to Western blotting. A dose-dependent increase in Bax levels was observed in the treated IOMM-Lee cells (Fig. 4). The overall amount of the Bcl-2 protein under similar conditions remained unchanged, leading to an increased Bax/Bcl-2 ratio, favoring the progression of apoptosis. In addition, decreased levels of survivin were also seen. The decreased survivin levels may also be a trigger for apoptosis. Our results indicate that combination therapy leads to a decreased Bcl-2/Bax ratio as well as decreased survivin levels in IOMM-Lee cells.

**Athymic Nude Mouse Model**

Athymic nude mice were subjected to subcutaneous implantation of IOMM-Lee human meningioma cells and divided into groups according to treatment received. Figure 5 demonstrates the average increase in tumor volume over time (in 6 animals ± SEs). At the end of the experiment on Day 23, the differences in tumor volume between the control group and all treatment groups reached statistical significance. Our results indicate that the combination of imatinib and nelfinavir leads to a significant reduction in tumor growth in the IOMM-Lee subcutaneous tumor model.

Tumor sections were obtained from drug-treated and untreated animals after 96 hours of treatment, and subjected to immunohistochemical analysis for the Bcl-2, Bax, GRP78, and survivin proteins. The TUNEL assay was used for the detection of apoptosis. Immunohistochemical results demonstrated that treated animals in the combination therapy group had higher levels of Bax and GRP78 and lower levels of survivin (Fig. 6) than untreated animals. There were also greater numbers of apoptotic cells in treated animal tumor sections (Fig. 6). These results are consistent with our in vitro results, suggesting that similar mechanisms of cytotoxicity are involved both in vitro and in vivo.

**Discussion**

Meningiomas are very difficult to treat using chemotherapy for several reasons. First, although they can reach a very large size and recur despite repeated surgical and radiosurgical procedures, the cells do not proliferate rapidly. As a result the standard cytotoxic chemotherapeutic agents that usually target rapidly proliferating cells may not be effective. Secondly, meningiomas have evolved defense mechanisms such as high levels of the antiapoptotic protein survivin. Last, although these cells have a number of membrane receptors, including estrogen, progesterone, and PDGF, effective targeting of these transmembrane receptors has been limited.

The ideal agent for the treatment of meningiomas is a well-tolerated drug with effectiveness on slowly proliferating cells that can be taken on a long-term basis. Ideally this drug should be cytotoxic; however, a low toxicity cytostatic drug could also be taken on a long-term basis. The importance of long-term suppression on slowly proliferating cells compared with rapid intravenous treatment on rapidly proliferating cells was recently highlighted in our work using irinotecan to treat meningiomas. Irinotecan was not demonstrated to be effective in a small pilot study of patients with recurrent nonmalignant meningiomas. This fact was well demonstrated in our preclinical study demonstrating that irinotecan was much more effective in a rapidly proliferating malignant meningioma cell line compared with its efficacy in primary cultures.
Although imatinib was not found to be effective as a single agent in the treatment of meningiomas, the oral availability, generally well-tolerated profile, PDGFR targeting, and cytotoxicity on meningioma cells make it a compelling agent. In this study, therefore, we investigated whether imatinib would be more effective in the treatment of meningiomas in combination with the protease inhibitor nelfinavir.

The in vitro efficacy of this treatment was established by MTT and colony formation assays in primary meningioma cells and in two meningioma cell lines, IOMM-Lee and CH157. A decreased cellular proliferation rate after combination treatment was observed in MTT assays. Similarly, colony formation assays, which indicate long-term drug treatment effects, demonstrated that the combination treatment led to decreased survival of tumor cells. Although the in-vitro doses used for the MTT assay are certainly higher than those in clinical studies, the in-vitro doses used for the colony formation assay are within the clinical range. Therefore, one reason for the higher drug concentrations used in the in vitro assays to demonstrate drug effects could also be a reflection of the type of assay used. Methylthiotetrazole assays require higher doses to achieve a drug inhibitory response compared with other assays such as the colony formation assay.

The antiapoptotic protein survivin is known to be highly expressed in benign brain tumors and may be responsible for the poor response of such tumors to standard chemotherapeutic treatment. In our experiments, we found that survivin levels were unchanged after imatinib treatment, but were decreased on nelfinavir treatment. Because increased survivin levels have been associated with resistance to imatinib treatment,

it is possible that the enhanced effects of the combination treatment are due to a potentiation of imatinib activity due to suppression of survivin when nelfinavir is added. Additionally, Bax levels were increased on combination treatment, while Bcl-2 levels remained the same. This change in the Bax/Bcl-2 ratio may be an additional mechanism whereby the tumors cells are directed towards the apoptotic pathway.

Results obtained from the in vivo assay corroborate our in vitro results. The IOMM-Lee tumors in mice were found to be smaller when treated with the combination of imatinib and nelfinavir, and had a reduced growth rate compared to untreated tumors or single agent imatinib or nelfinavir therapy. It is interesting to note that nelfinavir also has a significant negative effect on tumor growth, which is potentiated if higher doses of the drug are used (data not shown). The direct effect of nelfinavir as an anticancer agent has been corroborated in other studies as well. However, on the basis of drug dosage limits to human patients, it is unlikely that high doses of nelfinavir as a single agent would be tolerated. However, in combination with imatinib, nelfinavir has a more potent action. For the in vivo experiment, the drug doses used fall within the range of plasma drug concentrations that are seen in patients undergoing therapy with either drug.

Both imatinib and nelfinavir are well-tolerated medications that can be delivered orally. These are associated with minor side effects compared with those of cytotoxic chemotherapy or high-dose radiation therapy. Although cross-reactions between these two drugs given together are not known, no adverse effect on weight was observed in the course of our experiments in the animals that received both drugs. Because meningiomas lie outside the blood–brain barrier, it is expected that the oral delivery of these drugs will result in adequate drug concentrations. Nelfinavir has been used in long-term management of patients with acquired immunodeficiency syndrome, and has been well tolerated. It is also possible that the addition of nelfinavir would decrease the development of chemoresistance of the tumor to single-agent imatinib therapy. This paradigm may be extended to other imatinib-sensitive tumors, which may have developed resistance to imatinib after long-term treatment. Because meningiomas already have high survivin levels, we propose that combination therapy be used from the very start of the treatment. Ultimate clinical use of this therapy is dependent on a successful clinical trial in patients with primary unresectable or recurrent meningiomas. The positive aspects of the drugs used in the study are that they have been extensively studied and prescribed in the past, have an excellent safety profile, and can be orally administered. In view of the lack of chemotherapy options for unresectable, aggressive, or recurrent meningiomas, this combination therapy should be further evaluated as a potential addendum to surgery or radiation therapy in the care of such patients.
Conclusions

Combination imatinib and nelfinavir therapy may be a promising oral chemotherapy regimen for patients with both benign and malignant meningiomas. The addition of nelfinavir results in decreased survivin levels in meningiomas, increasing chemosensitivity to imatinib. Analysis of our initial laboratory data demonstrates that the combination of imatinib and nelfinavir may be an effective treatment for meningiomas; this finding will require substantiation by further studies.

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