Abstract

Purpose: Platelet-derived growth factor receptor β (PDGFRβ), frequently activated in malignant mesothelioma, is a promising cancer therapeutic target. Imatinib mesylate (STI571; Gleevec) is a selective inhibitor of tyrosine kinases as bcr-abl, c-kit, c-fms, and PDGFRβ and enhances tumor drug uptake by reducing the interstitial fluid pressure. We previously showed that imatinib mesylate synergizes with gemcitabine and pemetrexed in PDGFRβ-positive mesothelioma cells. Here, we aimed at investigating these combined treatments in a novel mesothelioma model.

Experimental Design: REN mesothelioma cells, infected with a lentiviral vector carrying the luciferase gene, were injected in the peritoneum of severe combined immunodeficient mice. This model allowed imaging of live animals treated with pemetrexed or gemcitabine chemotherapeutics, or with imatinib mesylate alone, as well as with a combination of gemcitabine and imatinib mesylate.

Results: We show here that, consistent with our previous in vitro studies, gemcitabine inhibited tumor growth, whereas pemetrexed was ineffective, even at the highest dosage tested. Compared with monotherapy, the combination of gemcitabine with imatinib mesylate led to a further tumor growth inhibition and improved mice survival, by a decrease rate of tumor cell proliferation and an increase in number of apoptotic tumor cells.

Conclusions: Imatinib mesylate enhances the therapeutic response to gemcitabine, in accordance with our previous in vitro data. These in vivo results validate imatinib mesylate and gemcitabine as a combination treatment of malignant mesothelioma, also in view of its known positive effects on tumor drug uptake. These evidences provide the rationale for the currently ongoing clinical trials.

Malignant mesothelioma is an asbestos-related malignant tumor, whose incidence will increase dramatically in the next decade (1). Due to its biological aggressiveness, the median survival is about 12 months, with a yearly death toll of 2,000 to 3,000 in the United States and about 1,000 in the United Kingdom (2). Hence, the urgency of new drug development to improve the clinical course of the disease.

The continuing increase in the incidence of malignant mesothelioma has been associated with the widespread use of asbestos in the past century. The mechanism of asbestos carcinogenesis has been linked to the activation of proinflammatory cytokines and nuclear factor-κB (3).

Only a fraction of about 5% of the subjects exposed to high levels of asbestos develop malignant mesothelioma (4). This finding suggests that additional factors, such as SV40 infection and genetic predisposition, may render these individuals to be more susceptible to asbestos carcinogenicity (5–7).

Moreover, SV40 and asbestos were shown to be cocarcinogens in hamster (8, 9) and caused malignant transformation of human mesothelial cells through activation of protein kinase B (10).

Interstitial hypertension is a feature of most solid tumors (11). The notion that increased interstitial fluid pressure (IFP) acts as a barrier for drug delivery into the tumor has recently found experimental support. Lowering of the IFP or, by other means, improving the transcapillary pressure gradient has been shown to increase the uptake of low molecular weight compounds, gases, and tumor-targeting antibodies (12). In some instances, it was further shown that the decrease in tumor IFP and the increase in tumor drug uptake were paralleled by an enhanced effect of anticancer therapy (13). Thus, there is

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Imatinib Mesylate Enhances Therapeutic Effects of Gemcitabine in Human Malignant Mesothelioma Xenografts

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mounting evidence that poor drug delivery from the bloodstream into the tumor interstitium can be augmented by adjuvant therapy with substances that lower the IFP.

Several findings underscore the crucial role of platelet-derived growth factor (PDGF) A and B in malignant mesothelioma cell growth (reviewed in 14). High expression level of PDGF receptor β (PDGFRβ) was shown in malignant mesothelioma cells, but not in normal human mesothelial cells, mostly expressing PDGFRα (15). Furthermore, increased expression of PDGF A and B were detected at higher levels in malignant mesothelioma cells compared with human mesothelial cells (16), and a significant reduction in malignant mesothelioma cell growth or migration was observed by blocking PDGF A and PDGF B (17). Many cytokines are released in the microenvironment by tumor stromal cells (18), and PDGF paracrine stimulation has been shown in human tumors and malignant mesothelioma in particular (19, 20). PDGFRβ activated by PDGF B can induce phosphorylation on-3-OH/protein kinase B signaling (21), which contributes to malignant mesothelioma cells survival (10). Inhibition of PDGFRβ was recently shown to lower the tumor IFP in different tumor models. The reduction in tumor IFP was paralleled by an increased tumor uptake of paclitaxel (Taxol) or epothilone B and a concomitant enhancement of the therapeutic efficacy (11–13). In mesothelioma, the extent of specimens positive for PDGFRβ expression range from about 30% to 45% in different studies (22, 23). Hence, large patient group might therefore benefit from therapeutic targeting of this signaling pathway.

Imatinib mesylate is a selective inhibitor for a subset of tyrosine kinases, including bcr-abl, c-Kit, PDGFRβ (24), as well as c-Fms (25). However, the therapeutic inefficacy of imatinib mesylate monotherapy for mesothelioma has been recently reported (22, 26), although we recently showed that imatinib mesylate synergizes with gemcitabine and pemetrexed selectively on PDGFRβ-positive mesothelioma cells (27).

Gemcitabine, cisplatin, etoposide, doxorubicin, and more recently, pemetrexed have been confirmed to be active for malignant mesothelioma treatment. Combined therapy of platin used with pemetrexed or gemcitabine has been shown to be more effective than each single agent alone (28).

On the other hand, combination therapies with imatinib mesylate yielded successful results in other human solid tumors grown in mice, indicating the involvement of PDGFRβ signaling in the regulation of tumor IFP and trans-vascular transport (13, 29). In the present preclinical study, we have investigated the effects of oral imatinib mesylate administration combined with i.p. injection of gemcitabine on the inhibition of the progressive growth of human malignant mesothelioma cells into the peritoneum of severe combined immunodeficient (SCID) mice.

Materials and Methods

Cell cultures. MMP mesothelioma cells were characterized and cultured as previously described (30). REN mesothelioma cells, kindly provided by Dr. Albelda (University of Pennsylvania, Philadelphia, PA), were cultured in Ham’s F-12 medium (Sigma) supplemented with 10% fetal bovine serum (Invitrogen) and maintained at 37°C in a 5% CO2–humidified atmosphere.

REN/luc luminescent cells and REN/green fluorescent protein fluorescent cells were derived from the REN cell line that was transduced with the lentiviral vector pRRL.sin.PPT.CMV, which was precarrying either a bioluminescent genetic marker (luciferase) or a fluorescent marker (green fluorescent protein).

Drugs. Imatinib mesylate was kindly provided by Novartis; gemcitabine and pemetrexed were provided by Lilly.

Animals. C.B-17-SCID or athymic nu/nu mice (female, 6-8 weeks old; Charles River) received i.p. injections of 1 x 106 mesothelioma cells (MMMP, REN, or REN-transduced cells) in 0.5 mL of Ham’s F-12 medium. To assess tumor dimension and localization of luminescent cells after anesthetization and i.p. injections of 0.3 mL of 15 mg/mL β-luciferin, bioluminescence signals of Ren/luc-inoculated mice were monitored using the IVIS system 100 series (Xenogen Corp.). Regions of interest were identified around the tumor sites and were quantified as total photon counts using Living Image software (Xenogen Corp.).

The values of tumor sizes were obtained, subtracting luminescence signals of each weekly measurement by the first measurement on the 10th day after inoculation, and these were expressed as the average of all values for every treatment group.

To evaluate the treatments toxicity, mice were weighed at the start and end of treatments. Mice were killed and necropsed when tumor developments caused severe ascites limiting the animals mobility. Survival was evaluated by the Kaplan-Meier method. Mice that were used for histologic studies were excluded from statistical analysis of death.

All animal experiments were done in accordance with institutional animal committee guidelines. Mice were maintained and handled under aseptic conditions, and animals were allowed access to food and water ad libitum.

Administration of drugs. An elapse of a period of 10 days was allowed for the formation of detectable tumor nodules by IVIS imaging. Mice were then weighed and stratified into each treatment group of seven animals. Treatment protocols were done from the 13th day to the 27th day, and mice were analyzed weekly by IVIS imaging to assess tumor growth until the 43rd day. Imatinib mesylate, alone or combined with gemcitabine, was given daily by oral gavage at 100 or 200 mg/kg as a single oral dose in 200 μL of PBS. Gemcitabine alone or in combination with imatinib was injected in different treatment groups i.p. at 120, 60, and 30 mg/kg every 3rd day for five doses, a regimen that was established previously as a well-tolerated dosage for SCID mice (31). Pemetrexed was injected in different treatment groups i.p. at 250 and 150 mg/kg on days 15th to 19th and 22nd to 26th, as previously reported in human tumor xenografts (32). Gemcitabine treatment started on the 3rd day after the beginning of imatinib treatment and, when injected on the same day, imatinib mesylate was given 1 to 2 h before chemotherapeutics (13). Control mice received i.p. injection of PBS and administration of DMSO, by oral gavage, diluted at 1:20 in water, as vehicles.

Necroscopy procedures for histologic studies. After tumor cell injection, at day 28th, one mouse from each group was killed and necropsied. Tumors growing in the peritoneum were excised, and one part of the tumor tissue was fixed in formalin and embedded in paraffin.

Immunohistochemical staining of proliferating cells and terminal deoxynucleotidyl transferase-mediated nick end labeling analysis. Sections were deparaffinized in xylene, dehydrated with alcohol, and rehydrated in PBS. Endogenous peroxidases were blocked with 3% hydrogen peroxide in PBS. After 1 h of incubation at room temperature with Kér7 antibodies (Neomarkers), biotin-streptavidin immunostaining was done with Ultravision (Labvision Co.) detection system, according to the manufacturer’s instructions. Apoptosis was evaluated in parallel sections by terminal deoxynucleotidyl transferase-mediated nick end labeling (TUNEL) analysis (DeadEnd Colorimetric TUNEL system; Promega). For quantification of Kér7 expression and apoptosis, the number of positive cells was counted in 10 random fields at ×300 magnification.

Statistical analysis. Tumor dimensions, body weight changes, Ki67-positive cells, and TUNEL-positive cells were compared using the
Results

Injection of engineered human mesothelioma cells allowed tumor imaging in SCID mice. To verify the efficacy of malignant mesothelioma xenografts, SCID or nu/nu (athymic, nude) mice were inoculated i.p. with $1 \times 10^6$ REN or MMP malignant mesothelioma cells, both expressing PDGFRβ. After 20 days, all SCID mice inoculated with REN cells developed abdominal palpable lumps. The autopsy confirmed the presence of histopathologically determined malignant mesothelioma in all animals. None of the nude mice nor SCID mice that were inoculated with MMP cells developed malignant mesothelioma. REN mesothelioma cells were transduced with a lentiviral vector, carrying either luciferase gene (REN/luc) or green fluorescent protein gene (REN/GFP), to allow imaging in live mice. After 30 days from inoculation, the animals were sacrificed. Autopsy revealed the occurrence of numerous peritoneal nodules (Fig. 1). IVIS imaging of malignant mesothelioma cells revealed a high fluorescence background in REN/GFP−inoculated mice. The detection of xenografts obtained with luciferase-transduced cells REN/luc was more sensitive and accurate. Therefore, we selected the REN/luc system for subsequent experiments.

Treatment with imatinib mesylate was ineffective on REN mesothelioma cell growth in SCID mice. The effects of treatment with imatinib mesylate were investigated on our newly established malignant mesothelioma model of SCID mice injected with REN/luc cells. Ten days after cell inoculation, tumor incidence in the peritoneal cavity was 100% in all treatment groups detailed below.

Two doses of imatinib mesylate were used (200 and 100 mg/kg). Interestingly, treatment with the higher dose (200 mg/kg) produced a significant increase of tumor dimensions compared with control-treated animals at each weekly observation ($P < 0.01$); however, survival was not influenced. Instead, a dose of 100 mg/kg imatinib mesylate did not induce any significant increase in tumor mass, compared with the control group, which also did not influence survival (Fig. 2A).

The toxicity of treatment regimens was assessed, evaluating changes of mice body weights during the drugs administration. Mice treated with 100 mg/kg of imatinib mesylate had weight gain comparable with controls. However, higher doses (200 mg/kg) resulted in a significant lower weight gain compared with controls ($P < 0.001$), suggesting toxicity (Table 1).

Survival rate was analyzed using the Kaplan-Meier method (Fig. 2B). These data indicated 100 mg/kg of imatinib mesylate as the more suitable dosage for combination therapies.

Pemetrexed is not effective on the malignant mesothelioma SCID mouse model. To investigate the efficacy of pemetrexed in our xenograft mesothelioma model, we stratified mice injected with REN/luc mesothelioma cells into the following three treatment groups: (a) control, vehicle alone; (b) 250 mg/kg pemetrexed alone; and (c) 150 mg/kg pemetrexed alone. We previously showed that REN mesothelioma cells respond to pemetrexed, with a LC$_{50}$ of about 50 μmol/L, whereas LC$_{50}$ for gemcitabine is about 40 nmol/L on the same cells (27). In vivo treatment with pemetrexed 150 mg/kg displayed a significant effect only at the end of the experiments ($P < 0.001$). Injection of 250 mg/kg pemetrexed surprisingly produced an unexpected significant increase of tumor mass compared with controls for the entire time span of the experiments ($P < 0.01$; Fig. 3A).

The toxicity of treatment regimens based on mice body weight changes is shown in Table 1. Pemetrexed given at 150 mg/kg led to an increase of mice body weight at lesser extent than vehicle treated mice ($P < 0.001$). The dose of 250 mg/kg induced a significant positive body weight variation compared with control animals ($P < 0.001$), but both treatments did not significantly improve survival (Fig. 3B). Despite the discrepancy from the established pemetrexed efficacy in mesothelioma treatment, these data were in accordance with our previous in vitro results where the REN mesothelioma cells were much more resistant to pemetrexed than gemcitabine (27). Moreover, the combination of pemetrexed at 250 mg/kg with

![Fig. 1. REN cells transduced with lentiviral vector induced recognizable tumors in SCID mouse. Necropsy of SCID mice inoculated with REN cells transduced with lentiviral vector carrying green fluorescent protein gene (A) or luciferase gene (B), after 56 d from implantation. Black arrows, tumor masses.](image-url)
200 mg/kg imatinib mesylate (E).

The results were compared with those obtained in the same experiment with mice injected with vehicle or gemcitabine alone at the same dosages.

Gemcitabine at 60 mg/kg significantly delayed tumor growth after the end of treatment (36th day), whereas the dosage of 30 mg/kg revealed a smaller growth delay with a significant tumor volume reduction only at the end of IVIS observations, on 43rd day after tumor inoculation (P < 0.001; Fig. 4A). Imatinib mesylate at 100 mg/kg combined with gemcitabine at 60 mg/kg caused a statistically significant suppression of tumor growth at the end of the observation period, compared with the gemcitabine monotreatment group (P < 0.001; Fig. 4A and C). Combination treatment of imatinib mesylate with the lowest effective dosage of gemcitabine of 30 mg/kg induced only a weak improvement of the chemotherapeutic drug effect, which was not statistically significant (data not shown). Body weight changes resulting from different treatments are illustrated in Table 1. The dosages of 60 and 30 mg/kg of gemcitabine, alone or combined with imatinib mesylate, did not cause any weight loss, in contrast to the weight loss caused by gemcitabine alone at 120 mg/kg. Mice treated with gemcitabine alone at 60 and 30 mg/kg did not reveal any survival improvement. Instead, combination of imatinib mesylate with gemcitabine at 60 mg/kg significantly improved the survival of treated mice (P < 0.01). At day 60, vehicle-treated mice displayed a severe ascite, whereas the ascite of mice under this combined treatment was clearly reduced, in accordance with data on tumor dimensions (Fig. 4B and D). Survival of mice treated with imatinib mesylate in combination with the lowest effective dose of gemcitabine (30 mg/kg) was not modified, compared with monotherapy at the same dose (data not shown).

These results are consistent with those recently observed in vitro (27) and clearly indicate that in vivo combination of imatinib mesylate plus gemcitabine 60 mg/kg leads to an improved antitumor activity, compared with the antitumor activity of each agent alone.

Histopathologic analysis of cell growth and apoptosis in human mesothelioma xenografts. Tissues from tumors growing in the

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body weight variation (%)</th>
</tr>
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<tbody>
<tr>
<td>Vehicle</td>
<td>+ 8.71 ± 0.24</td>
</tr>
<tr>
<td>200 mg/kg imatinib mesylate</td>
<td>+ 4.32 ± 0.18</td>
</tr>
<tr>
<td>100 mg/kg imatinib mesylate</td>
<td>+ 14.47 ± 0.42</td>
</tr>
<tr>
<td>120 mg/kg gemcitabine</td>
<td>- 13.41 ± 0.21</td>
</tr>
<tr>
<td>60 mg/kg gemcitabine</td>
<td>+ 12.70 ± 0.31</td>
</tr>
<tr>
<td>30 mg/kg gemcitabine</td>
<td>+ 6.22 ± 0.17</td>
</tr>
<tr>
<td>250 mg/kg pemetrexed</td>
<td>+ 16.51 ± 0.34</td>
</tr>
<tr>
<td>150 mg/kg pemetrexed</td>
<td>+ 6.27 ± 0.13</td>
</tr>
<tr>
<td>60 mg/kg gemcitabine + 100 mg/kg imatinib mesylate</td>
<td>+ 9.52 ± 0.24</td>
</tr>
<tr>
<td>30 mg/kg gemcitabine + 100 mg/kg imatinib mesylate</td>
<td>+ 9.49 ± 0.12</td>
</tr>
</tbody>
</table>

*Mice were weighed before and after treatments to evaluate resultant toxicity. Data are expressed as the mean percentage of weight change ± SE.
mice peritoneum were excised, formalin fixed, paraffin embedded, and analyzed for cell proliferation and apoptosis. Cell proliferation was evaluated by Ki67 staining (proliferating cell nuclear antigen). In tumors from control mice, the median number of Ki67-positive cells was 17.9 ± 3.0. Treatment with imatinib mesylate at 100 mg/kg alone or gemcitabine at 60 mg/kg alone did not alter the number of dividing Ki67-positive cells, whereas a significant decrease of Ki67-positive cells was found in tumors treated with combination regimens, compared with chemotherapeutic monotreatments at 250 mg/kg (▲), 150 mg/kg (▼), or with vehicle (○). A, survival analysis on groups of mice treated with pemetrexed at doses of 250 mg/kg (▲) or 150 mg/kg (▼) compared with vehicle treatment (○).

The evaluation of apoptosis in the malignant mesothelioma mice tumors was done by TUNEL assay. In tumors from vehicle-treated mice, the median number of apoptotic tumor cells was minimal (3.4 ± 0.8). The number of apoptotic cells in tumors from mice treated with imatinib mesylate given alone was not significantly different from control mice tumors. Therapy with gemcitabine at 60 mg/kg given alone induced a significant increase of apoptotic cell number when compared with vehicle injection (P < 0.001), and combination with imatinib mesylate further significantly improved this figures (P < 0.05; Fig. 5).

Discussion

In this article, using a new animal model of human malignant mesothelioma, we show that the combination of gemcitabine with a specific tyrosine kinase inhibitor can enhance the efficacy of mesothelioma treatment. We recently reported that imatinib mesylate synergizes with gemcitabine and pemetrexed selectively on PDGFRα-positive mesothelioma cells (27). The results shown here confirm our preclinical results obtained in vitro and provide further evidences with relevant translational implications. To validate this novel approach to malignant mesothelioma therapy, we established a mouse model injecting REN mesothelioma cells on the peritoneum of SCID mice, carrying either a luciferase gene or a green fluorescent protein gene to allow imaging by IVIS imaging system.

A major advantage of a marking system using a charged coupled device camera is the ability to evaluate tumor dimension changes sequentially over time in the same living animal. This ability obviates the need to euthanize multiple cohorts of animals at each required time point. This approach reduces potential animal-to-animal variance and allows long term studies (34).

Studies in vivo on malignant mesothelioma showed that percentage of positive specimens for PDGFRα expression is in the range of 30% to 45%, depending on the different studies (22, 23). Either autocrine or paracrine mechanisms may cause the activation of PDGFRα in vivo. Several autocrine loops have been described as an activating mechanism leading to tyrosine kinase receptor activity in malignant mesothelioma cells (30, 35, 36), and stromal microenvironment has been shown to be a fundamental source of activating ligands for PDGFR in human tumors (18). We have shown that tyrosine phosphorylation of PDGFRα in MMP and REN cells is inhibited by imatinib mesylate, leading to cytotoxic effects (27).

Preclinical studies on several human solid tumors revealed the efficacy of imatinib mesylate as a cytotoxic agent (37, 38). In opposition, two recent negative reports gave clear evidence that imatinib mesylate monotherapy is ineffective for malignant mesothelioma (22, 26). On the other hand, combined therapy of imatinib mesylate with different chemotherapeutic agents has been shown effective. A number of studies reported a decreased interstitial hyper pressure in tumor stroma provoked by the imatinib mesylate inhibition of PDGFR signaling, which in turn improves the drug delivery, enhancing the effects of chemotherapeutic reagents (11–13, 29).

In analogy to the previous clinical observations (22), we show here that imatinib mesylate as a single treatment has limited effect on the inhibition of tumor growth and prolongation of survival. On the other hand, the combination of imatinib mesylate with gemcitabine significantly lowers the number of Ki67-positive cells and increases the number of apoptotic tumor cells, causing inhibition of tumor growth and prolonged survival. This therapeutic effect was significantly more efficient than that of gemcitabine monotherapy. Furthermore, in the regimens where gemcitabine was well-tolerated, imatinib
Mesylate treatment did not cause toxicity, compared with gemcitabine monotreatments, as judged by body weight.

In conclusion, previous findings from our group and others (10, 13, 27, 29) showed that imatinib mesylate inhibited PDGFRβ, which in turn led to protein kinase B inactivation, resulting in malignant mesothelioma cell sensitization to low chemotherapeutic concentrations. The previously established synergism in vitro was improved in vivo where imatinib mesylate is presumably also able to decrease the tumor IFP, therefore increasing the uptake of cytotoxic drugs into the

Fig. 4. Imatinib mesylate enhances gemcitabine therapy in human mesothelioma xenografts. A, tumor inhibition by 60 mg/kg gemcitabine combined with imatinib mesylate (○) compared with vehicle (□) and gemcitabine given alone at 60 mg/kg (▲) and 30 mg/kg (▼). B, survival analysis of SCID mice treated with vehicle (□), 60 mg/kg gemcitabine (▲), 30 mg/kg gemcitabine (▼), or 60 mg/kg gemcitabine combined with 100 mg/kg imatinib mesylate (●). C, REN/luc cells were i.p. inoculated into SCID mice on day 0. Treatments were from 13th day to 27th day, and mice were analyzed weekly by IVIS imaging to assess tumor growth. After 43 d, IVIS imaging system showed that combined treatment with gemcitabine 60 mg/kg and imatinib mesylate 100 mg/kg partially suppressed tumor growth on the peritoneal cavity compared with control mice. D, on 60th day, vehicle-treated mice (left) have severe ascite compared with mice under combined treatment (60 mg/kg gemcitabine – 100 mg/kg imatinib mesylate; right).
tumor stroma. Consequently, our successful results on the novel human malignant mesothelioma animal model, confirming our in vitro findings, show that imatinib mesylate enhances gemcitabine effects on malignant mesothelioma.

The proof of principle established by our present work and by a clinical pilot study allowed us to design a phase II clinical trial currently ongoing.

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