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Increased Serum Insulin-like Growth Factor-1 Levels are Associated with Prolonged Response to Dasatinib-based Regimens in Metastatic Prostate Cancer

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Abstract

Background—Dasatinib, an inhibitor of Src-family kinases, combined with docetaxel in men with castrate-resistant prostate cancer (CRPC), affects bone turnover markers in a phase I/II clinical trial in metastatic CRPC. Only a subset of men benefit from this therapy, and predictive markers are lacking. We hypothesized a role for insulin-like growth factor-1 (IGF-1) as a predictive marker, since IGF-1 is important in both prostate cancer progression and bone development. Hence, we determined the association of IGF-1 expression to treatment response, and whether this expression resulted from tumor cells, the microenvironment, or their interactions.

Methods—We measured serum IGF-1 levels in men with CRPC treated with dasatinib plus docetaxel. To investigate the source of IGF-1, we utilized two different mouse models harboring human prostate cancer cells, and used species-specific IGF-1 ELISA kits (mouse vs. human).

Results—In men with CRPC, an increase in IGF-1 levels after one cycle of treatment with dasatinib and docetaxel is associated with a higher response rate and longer duration of treatment. Xenograft experiments with subcutaneous and intratibial injection of prostate cancer cells suggest that direct interaction of prostate cancer cells with bone microenvironment is necessary for IGF-1 induction, is entirely host-derived, and occurs only in mice that respond to dasatinib-based therapy.

Conclusion—Our results support a role for serum IGF-1 as a potential biomarker for benefit from dasatinib-based combination treatments in CRPC.

Keywords

predictive marker; Src inhibition; bone microenvironment; docetaxel; xenograft

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Introduction

Castration-resistant prostate cancer (CRPC) is associated with high morbidity and mortality in men afflicted with this disease, the majority of whom will develop bone metastasis and die from complications from these metastases[1]. Recent advances in our understanding of the biology of CRPC highlight the necessity to interrupt the vicious cycle of the interaction between prostate cancer cells and their surrounding bone microenvironment (i.e. osteoblasts, osteoclasts etc.)[1,2]. Within this conceptual framework, the non-receptor tyrosine kinase Src has been implicated as an important target in prostate cancer bone metastases, since it promotes invasion, migration and metastasis of prostate cancer cells[1,3,4], and is critical to osteoclast function. In addition, the Src family kinase (SFK) small molecule inhibitor, dasatinib, has been shown to decrease proliferation of immature osteoblasts while enhancing their differentiation [5]. Based on these findings, trials combining dasatinib with the cytotoxic agent docetaxel have been completed in men with CRPC. In the early phase study [6], a small subset of men exhibited encouraging results with prolonged disease control when maintained on dasatinib alone (more than 30 months with no detectable PSA), while others progressed relatively quickly on this combination [6]. In that study, change in serum turnover markers bone alkaline phosphatase (BAP) and urinary N-telopeptide (uNTx) corresponded with clinical response, supporting the hypothesis that dasatinib-based therapy as well as having an impact on the tumors themselves in prostate cancer also modulates the bone microenvironment. Given the striking difference between men with prolonged clinical benefit on dasatinib and those that do not respond, it will be extremely important to identify biomarkers that would distinguish between these groups, which could in the future provide a basis for patient-selection.

Insulin-like growth factor-1 (IGF-1) has been implicated in prostate cancer progression in epidemiologic studies, and work from our group and others have established the IGF-1/IGF-1R pathway as a significant target in prostate cancer [7,8,9,10,11,12]. Higher IGF-1 levels confer a higher risk for developing prostate cancer and are associated with an advanced stage [13,14]. Importantly, signaling through IGF-1R affects androgen receptor activation and transcriptional profile [15,16]. Furthermore, IGF-1 is crucial for osteoblast differentiation and found abundantly in the bone microenvironment[17]. Thus, while IGF-1 activates signaling pathways that promote tumor progression, it also potentially maintains the “vicious cycle” by differentiating osteoblasts. Therefore, we determined if modulation of serum IGF-1 levels might correlate with response to dasatinib-based therapy in prostate cancer. Using murine models and primary patient samples, we determined that tumor/bone interactions are necessary for IGF-1 expression and most of the IGF-1 results from the host microenvironment. These results identify IGF-1 as a potential predictor for response to dasatinib-based treatments in CRPC.

Material and Methods

Cell lines

PC3 cells were purchased from ATCC and the osteoblast precursor cell line MC3T3-E1 was kindly provided by Dr. Sue-Hwa Lin (MD Anderson Cancer Center, Houston, TX). MC3T3-

E1 cells were grown and differentiated as previously described [5]. All cells were checked every six months and found to be mycoplasma free, and cell typing analysis was performed by the M.D. Anderson Cancer Center Cell Identification core to ensure fidelity of the cell lines used. Maturation to osteoblasts was determined by measuring alkaline phosphatase activity in the cell extracts as previously described, using p-nitrophenyl phosphate liquid substrate system (Sigma)[5]. During the last three days of differentiation, PC3 cells were added to MC3T3-E1 cells and co-cultured for 72 hours. Then, the supernatant was collected, centrifuged, and stored at -20°C.

Small molecule inhibitors

The IGF-1R/IR (insulin receptor) inhibitor BMS-754807 was provided by Dr. J. Carboni (Bristol-Myers Squibb, BMS), and dasatinib was provided by Dr. J. Araujo (MD Anderson Cancer Center).

Patient samples

The details of the phase I/II clinical trial of docetaxel and dasatinib in men with CRPC were published elsewhere[6]. In brief, men with CRPC and documented metastasis received docetaxel (75 mg/m² i.v.) once every 21 days. Dasatinib was given at 100mg P.O. once daily starting day 3 of cycle 1, and continued until disease progression (i.e. dasatinib was continued beyond docetaxel treatment in patients who did not progress). PSA response was defined as a confirmed decrease of serum prostate specific antigen of greater than 50%. Serum was collected on cycle 1, day 1 before any drug was given and then again on day 21, i.e. after 18 days of treatment with dasatinib. All patients had given written informed consent, and the study was approved by the Institutional Review Board. Samples were stored at -80°C until analysis. Serum or plasma levels of IGF-1 and prolactin were measured using specific Luminex beads (AssayGate) following the manufacturer's recommendations. Each measurement was performed in duplicate and the average was calculated.

In vitro and in vivo IGF-1 level determination

Quantitative determination of human and murine IGF-1 from mouse sera and cell culture supernatants was performed using the respective Quantikine® ELISA (R&D Systems) according to the manufacturer's instructions. All standard curves had a R² of 0.990. Positive controls for each assay were provided by the manufacturer.

Xenografts

All animal studies were approved and according to the guidelines of the Institutional Internal Review Board at M.D. Anderson Cancer Center. Intratibial injection of PC3-MM2 cells was performed as described previously [18] and the primary results are reported elsewhere[7]. In brief, 0.5x10⁶ PC3-MM2 cells were injected into the tibiae of nude mice (n= 10/group). Two weeks after injection, the mice were treated daily by oral gavage with saline, dasatinib (12.5mg/kg), BMS-754807 (12.5mg/kg), or a combination of both drugs. Two weeks after treatment, the mice were euthanized and serum was collected and stored at -20°C. X-rays were taken from the long bones and the amount of bone destruction (PC3-MM2 cells form osteolytic tumors) was graded in a blinded fashion as described elsewhere[7]. Briefly, x-rays

of the bones were taken at the time of euthanasia, and osteolytic lesions and soft tissue tumor formation were graded from “0” (i.e. no radiographic changes) to “3” (i.e. complete destruction of the bone and large tumor formation).

To examine potential bone-independence of IGF-1 production 0.5×10^6 PC3 cells were injected subcutaneously (SubQ) as described previously [3]. Tumor volume *in vivo* was calculated as described previously [7]. Two weeks after injection, the mice with SubQ xenografts were treated by oral gavage with dasatinib and/or BMS-754807 at the doses above for two weeks.

Statistics

The Student's t-test was used to compare differences between the two groups. A <0.05 was considered statistically significant.

Results

Changes of serum IGF-1 levels in mice treated with dasatinib-based regimens

We have recently shown data on intratibial tumor growth of the aggressive PC3-MM2 cell line in mice treated with a combination of dasatinib, an SFK inhibitor, and BMS-754807, a dual IGF-1R/IR (insulin receptor) inhibitor, demonstrating enhanced tumor inhibition with the combination of both drugs [7]. In anticipation of a clinical trial with this combination in men with CRPC, we tried to identify potential useful biomarkers for dasatinib-based therapies. Since dasatinib is a modulator of the bone microenvironment and IGF-1 is abundant in the bone milieu, we hypothesized modulation of bone-prostate cancer interactions might correlate with changes of measurable serum IGF-1. To evaluate the potential role of serum IGF-1 as a predictor of response to dasatinib-based treatments, we used serum from those mice treated with dasatinib, BMS-754807, or the combination after intratibial injection of PC3-MM2 cells. X-rays of the mice (to evaluate tumor progression) were taken and serum samples were collected at the time of euthanasia. Response criteria have been described elsewhere and essentially include grading of bone destruction and soft tissue mass on x-rays of the mice, as also explained in the Methods [7]. To correlate IGF-1 levels with treatment responses in the mice, we checked both human and murine IGF-1 levels in all mice. Serum ELISA for murine and human derived IGF-1 showed a significant increase of murine IGF-1 by about 30% in the mice treated in the combination group compared with single agent and saline only groups. In contrast, the levels of human IGF-1 remained below the detection level in all four groups, indicating the increase of IGF-1 is host-derived (**Fig. 1A**). We noted that the increase in serum IGF-1 was observed only in those mice with a radiographic response to the combination therapy, since the mice in the combination group who did develop tumors had serum IGF-1 levels comparable to the control cohort (control cohort) (Fig. 1B). This finding suggests that the increase of host-derived IGF-1 levels is not simply a pharmacologic effect of the combination of both drugs, but rather specific to tumor response in this model.

Since there was no measurable circulating human IGF-1, we concluded that the increase in measured IGF-1 by the host was either from paracrine production in the microenvironment irrespective of tumor location, or from paracrine production from bone cells after interaction with tumor cells. To distinguish these two possibilities, PC3 cells were injected subcutaneously and mice were either treated with dasatinib, BMS-754807, or the combination, for 14 days (same regimen as described in the intratibial experiment). As shown in **Fig.2A**, tumors treated with dasatinib plus BMS-754807 had a slower growth rate with a significantly smaller increase in tumor size after 2 weeks treatment (**Fig. 2B**). However, tumor implantation did not result in a change in murine IGF-1 between the treatment groups, unlike what was observed in the bone, suggesting tumor/bone interactions are required for increased IGF-1. Further, human IGF-1 was beneath the level of detection (data not shown). Based on these results, we conclude that IGF-1 induction does not occur in a non-bone microenvironment.

IGF-1 is secreted by differentiated osteoblasts but not prostate cancer cells

IGF-1 has been reported to be secreted by osteoblasts[17]. To determine if osteoblasts were the likely source of IGF-1 in our studies, we cultured the murine osteoblast precursor cell line MC3T3-E1 in presence of differentiation media to induce mature osteoblasts [5]. Once the cells were differentiated (as measured by alkaline phosphatase production [5]; **Fig. 3A**), human PC3 cells were added to the culture and incubated for 72 hours, followed by harvesting of the supernatant. As shown in **Fig. 3B**, differentiation of MC3T3-E1 cells led to a significant increase in IGF-1 production in the supernatant. The addition of PC3 cells led to a modest decrease in IGF-1. Again, as observed in the murine *in vivo* model, no significant amounts of human IGF-1 were detected, suggesting that in this system, and likely in the human tumors above, measureable IGF-1 is host derived.

Time on treatment with dasatinib-based therapy correlates with IGF-1 serum levels in men with CRPC

To test whether our preclinical findings have any potential relevance to patients with prostate cancer, our next aim was to examine serum IGF-1 levels in men with CRPC treated with a dasatinib based regimen. Since BMS-754807 has not yet been tested with dasatinib in patients with CRPC, we had to identify another treatment combination available for analysis. Thus, we used serum samples from patients with CRPC with bone metastases who were treated on a phase I/II protocol with dasatinib and docetaxel [6]. We have previously shown that BMS-754807 induces apoptosis in prostate cancer cells and thus functions as a 'cytotoxic' agent[7], similar to the effects of docetaxel[19]. Using the official study documents, we determined for each patient (n=19) the duration of time on study (in weeks), since this corresponded with the total time of treatment with dasatinib (patients continued to receive dasatinib after docetaxel was stopped if they disease had not progressed). The median duration of therapy for all patients was 31 weeks. **Fig. 4A** shows the relative change in serum IGF-1 levels (day 21 vs day 1) for the cohort treated on study >31 weeks compared to those ≤31 weeks. Surprisingly, after one cycle of treatment, serum IGF-1 levels significantly increased in men who remained longer on trial (i.e. they benefited more from treatment), whereas for men below the median there was no change or a trend towards a decline in IGF-1 levels ($P=0.029$ for treatment >31 weeks vs ≤31 weeks). As a control, we

compared the change in serum levels of prolactin. As expected, there was no significant difference in the change of prolactin levels between the two groups (**Fig. 4B**; $P=0.63$). When comparing the top 25th with the bottom 25th percentile, the difference was even more significant ($P=0.0003$). Furthermore, 8 of 9 (88.9%) of the men in the above-median cohort had a PSA response vs. 5 of 10 (50%) in the below-median cohort.

Discussion

The IGF-1/IGF-1R axis is emerging as an important target in prostate cancer and other solid tumors. Several new inhibitors of this axis are currently being investigated in clinical trials. IGF-1 levels have been associated with prostate cancer progression[9,20,21], and IGF-1 is found abundantly in the bone microenvironment[17], the most significant site for prostate cancer metastasis. However, the source of the available IGF-1 is not well understood, and might have predictive and prognostic implications. Therefore, the central focus of this study was to determine the source of IGF-1 (tumor, microenvironment or both). In our intratibial xenograft model, we showed the combination of dasatinib with BMS-754807 resulted in a 30% increase in host-derived IGF-1. This increase was similar to the increases seen in patients with CRPC and bone metastases treated with dasatinib and docetaxel, suggesting the mouse model we were using mimicked the human disease. Considering that the major source of circulating IGF-1 is the liver[22], a bone-derived 15-30% increase in total circulating IGF-1 is also clinically significant since it implies a much higher induction of IGF-1 in the bone microenvironment. Furthermore, our data indicate the increase in IGF-1 is not merely a pharmacologic effect of a specific drug combination since a) the increase in IGF-1 in mice treated with both dasatinib and BMS-754807 was seen only in those mice with a tumor response, and b) the association between response and rise in IGF-1 levels was seen in two independent models (murine and human) with two different dasatinib-based combinations (BMS-754807 and docetaxel, respectively). The source of IGF-1 was identified as host-derived based on our ability to use different IGF-1 ELISA kits for human and murine IGF-1. Finally, ectopic xenograft experiments with PC3 cells growing subcutaneously did not affect IGF-1 levels, indicating that likely a direct interaction between tumor cells and their bone microenvironment is necessary to induce IGF-1.

Dasatinib has been evaluated in CRPC clinical trials as single agent as well as in combination with other agents such as docetaxel [1,6,23,24]. Whereas dasatinib as monotherapy has only modest antitumor effects [23,24], combination regimens with dasatinib and cytotoxic agents have shown more promise of clinical activity [6,25]. We have shown that the IGF-1R/IR inhibitor BMS-754807 inhibits prostate cancer cells mainly through induction of apoptosis[7], and thus may be regarded as a "cytotoxic" agent. A large randomized phase III trial of dasatinib and docetaxel has finished accrual, and the overall survival results are pending [[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00744497) Identifier: NCT00744497]. From the experience with the preceding phase I/II trial [6], it is clear that subsets of patients with CRPC will benefit from the addition of dasatinib while others will not. Unfortunately, there is a paucity of candidates of possible predictive serum biomarkers for clinical benefit from dasatinib in prostate cancer and other solid tumors. In this context, we believe our study identified a promising marker that can be easily measured in patients' blood samples, and at most medical centers is available as a routine test in clinical laboratories. It is necessary to

obtain independent validation of the observed effects in a larger cohort of patients. One such possibility would be to correlate the change in IGF-1 serum levels to treatment duration in the large cohort of men enrolled on the phase III trial of docetaxel with or without dasatinib (n=1500) once the results become available [[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00744497) ID: NCT00744497].

Conclusion

Host-derived serum IGF-1 levels increase when there is a bone response to combination regimens of dasatinib and cytotoxic agents in CRPC. The role of IGF-1 as a potential predictive marker in CRPC should be validated in a prospective manner and might be useful in the future to personalize treatment of men with CRPC.

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Figure 1.
Induction of host-derived serum IGF-1 by dasatinib-based combination is dependent on tumor response in the bone microenvironment .

Figure 2.
Paracrine tumor effects are not sufficient to induce IGF-1 in response to dasatinib-based combination therapy.

Figure 3.
In vitro maturation induces IGF-1 production in osteoblasts but not in co-cultured prostate cancer cells.

Figure 4.

An increase in serum IGF-1 is associated with prolonged benefit from dasatinib-based combination therapy in men with CRPC.