ORIGINAL ARTICLE

Biomarker-Integrated Neoadjuvant Dasatinib Trial in Resectable Malignant Pleural Mesothelioma

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ABSTRACT

Introduction: Window of opportunity trials in malignant pleural mesothelioma (MPM) are challenging but can yield important translational information about a novel agent.

Methods: We treated patients with MPM (N = 24) with 4 weeks of oral dasatinib followed by surgery with or without radiotherapy and then an optional 2 years of maintenance dasatinib. The primary end point was biomarker modulation of phosphorylated (p) Src^{Tyr419}.

Results: For all patients, the median progression-free survival (PFS) was 7.5 months and the median overall survival was 19.1 months. No significant responses were seen after 4 weeks of dasatinib therapy; however, modulation of median p-Src^{Tyr419} immunohistochemistry (IHC) scores was seen: the median pretreatment score was 70 (interquartile range 37.5–110), and the median posttreatment score was 41.9 (interquartile range 4.2–60) ($p = 0.004$). A decrease in p-Src^{Tyr419} levels after dasatinib correlated with improved median PFS (6.9 months versus 0.94 months [$p = 0.03$]), suggesting that p-Src^{Tyr419} is a viable pharmacodynamic biomarker for dasatinib in MPM. Platelet-derived growth factor receptor (PDGFR) pathway analysis correlated high PDGFR beta [PDGFRB] level (in the cytoplasm [hazard ratio] (HR) = 2.54, $p = 0.05$], stroma [HR = 2.79, $p = 0.03$], and nucleus [HR = 6.79, $p = 0.023$]) with a shorter PFS. Low (less than the median) cytoplasmic p-PDGFR alpha IHC levels were predictive of a decrease in positron emission tomography/computed tomography standard uptake values levels after dasatinib therapy ($p = 0.04$), whereas higher-than-median IHC scores of PDGFRB (cytoplasmic [HR = 2.8, $p = 0.03$] and nuclear [HR = 6.795, p = 0.02]) were correlated with rising standard uptake values levels.

Conclusions: In conclusion, there was no significant efficacy signal, and dasatinib monotherapy will not continue to be studied in MPM. However, our study demonstrated that PDGFR subtypes (platelet-derived growth factor receptor alpha and PDGFRB) may have differential roles in prognosis and resistance to antiangiogenic tyrosine kinase inhibitors

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and are important potential therapeutic targets that require further investigation.

Keywords: Mesothelioma; Dasatinib; Src kinase; Platelet-derived growth factor receptor

Introduction

Malignant pleural mesothelioma (MPM) is an orphan disease with few treatment options. In the small proportion of patients who are candidates for aggressive surgical resection, the median survival duration with multimodality therapy remains grim at around 17 months.[1] Recent trials of induction therapy with platinum doublets report higher survival in responders, but these trials were small and not randomized.[1–5] Nevertheless, they imply that more effective systemic therapies can improve patient survival outcomes; thus, identifying targetable biomarkers predictive for response to systemic agents is critical in this disease.

Src is a non–receptor tyrosine kinase that is associated with tumor cell invasion, proliferation, angiogenesis, and antiapoptosis.[6–8] Src-associated biological effectors such as metalloproteinases, E-cadherin, and integrin-dependent complexes promote tumor cell invasion,[9] whereas platelet-derived growth factor receptor (PDGFR)[8,10–12] activates tumor cell proliferation. Src kinase is stimulated by vascular endothelial growth factor receptor[13] and the hypoxia pathway HIF-1α, which increases vascular endothelial growth factor receptor expression.[8,13]

We previously demonstrated that Src kinase is commonly expressed and activated in MPM cell lines and tissue samples by phosphorylation at the activation Src^{Tyr419} site (phosphorylated [p]-Src^{Tyr419}).[14,15] Our prior immunohistochemistry (IHC) study of 46 surgically resected mesothelioma paraffin-embedded tissue specimens demonstrated that p-Src^{Try419} expression was present in 43% of tumor membranes and 67% of tumor cytoplasms.[15] Positive p-Src^{Tyr419} IHC expression was associated with more advanced disease and greater likelihood of metastatic disease.[15]

Dasatinib (BMS-354825, Bristol-Myers Squibb, New York, NY) is a broad-spectrum adenosine triphosphate–competitive inhibitor of five oncogenic tyrosine kinases/kinase families (BCR-ABL; SRC; c-Kit; PDGFR, PDGFR alpha [PDGFRA], and PDGFR beta [PDGFRB]; and ephrin receptor kinases). Our preclinical studies demonstrated that dasatinib had target specificity to p-Src^{Tyr419} in mesothelioma cell lines and prevented cell proliferation and invasion.[15] However, dasatinib's mechanism of action may not be limited to Src kinase inhibition, as it may also affect MPM cells and tumors through the PDGF/PDGFR pathway. MPM tumor cells express platelet-derived growth factor (PDGF) and PDGFR[16–22] and use this pathway as an autocrine loop mechanism for tumor cell proliferation and angiogenesis.[17–19,23–25]

We therefore hypothesized that dasatinib would be an effective therapeutic agent in MPM and that the p-Src^{Tyr419} and PDGF/PDGFR pathway biomarkers would be predictive of clinical outcomes. We sought to test our hypothesis by treating patients with resectable MPM with neoadjuvant dasatinib therapy in a window of opportunity biomarker study. The primary end point was identification of the prognostic and predictive value of p-Src^{Tyr419} IHC and determination of the extent to which dasatinib modulated the biomarker. Window of opportunity trial assessments in MPM are complex—namely, there are controversial issues of whether MPM surgery (extrapleural pneumonectomy [EPP] or pleurectomy/decortication [P/D]) is beneficial, whether the variable administrations and therapeutic durations of adjuvant novel agents can affect survival, and whether the use of a molecular end point for the primary objective in trials can be valid and translatable to the clinic. However, this trial platform enables a pure assessment of a novel targeted agent and relevant tumor biomarkers.

Methods

Patients, Trial Schema, and Samples

This single-arm institutional review board–approved study (NCT00652574) enrolled patients with potentially resectable (by P/D or EPP) MPM treated at The University of Texas M. D. Anderson Cancer Center between 2008 and 2012. Patient eligibility criteria were age at least 18 years, epithelioid or biphasic histologic type (nonsarcomatoid), resectable disease, no comorbid conditions precluding surgical resection, and chemotherapy-naive status. Patients with untreated MPM underwent extended surgical staging (ESS)[26] with multiple biopsies to account for tumor heterogeneity. Each tumor biopsy specimen removed from the patient was cut in half, with one part flash-frozen and the second part formalin-fixed for paraffin. If deemed surgical candidates for either P/D or EPP, patients received 4 weeks of neoadjuvant dasatinib (70 mg orally twice a day) until the day before surgical resection.

Safety and toxicity were monitored weekly by using the National Cancer Institute Common Toxicity Criteria (version 3.0). The clinical outcomes evaluated were the response rate at 4 weeks by positron emission tomography (PET)/computed tomography (CT) scan, progression-free survival (PFS), and overall survival (OS). PET/CT standardized uptake value (SUV) levels and anatomic tumor measurements by modified Response Evaluation Criteria in Solid Tumors (RECIST) were performed. SUV levels for