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A phase II trial of dovitinib in previously-treated advanced pleural mesothelioma: The Ontario Clinical Oncology Group

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ABSTRACT

Objectives: Following failure of a platinum-antifolate combination regimen, there is no standard therapy for advanced malignant pleural mesothelioma (MPM). The fibroblast growth factor receptor (FGFR) signaling pathways may be a relevant target in MPM. Dovitinib inhibits multiple tyrosine receptor kinases, predominantly the vascular endothelial growth factor receptors (VEGFR), but also FGFRs, and could be active in MPM.
Methods: This open-label multicentre phase II trial [NCT01769547] enrolled fit, consenting adult patients with advanced MPM who had previously received platinum-antifolate combination chemotherapy and up to one additional line of systemic therapy. Dovitinib was administered orally at 500 mg/day for 5 days on, 2 days off, in 28-day cycles. Response was assessed every 2 cycles using RECIST 1.1 criteria modified for MPM. Correlative studies included FGFR-1 amplification on archival tumour and serum samples for circulating angiogenesis factors. The primary end-point was the proportion of patients progression-free at 3 months (PF3) using a two-stage design.
Results: 12 patients (10 males, median age 67) were enrolled. The median number of cycles administered was 2.5 (range 1–8). One unconfirmed partial response was observed. PF3 was 50% (95% confidence interval 28.4% to 88.0%); although the criterion for proceeding to stage II accrual was met, the trial was halted due to a combination of minimal activity with several early progression events and poor tolerability in this patient population. One of 12 tumour specimens had low amplification of FGFR-1.
Conclusions: Dovitinib has minimal activity in previously-treated MPM. The role of the FGFR pathway in MPM remains unclear.

1. Introduction

Malignant pleural mesothelioma (MPM) presents with advanced, incurable disease in the majority of patients. The combination of cisplatin with an anti-folate, either raltitrexed [1] or pemetrexed [2], is standard first-line chemotherapy. In select patients, the addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF)-A, has been shown to lead to modestly improved outcomes [3]. Patients with MPM have among the highest levels of circulating angiogenesis factors, such as VEGF when compared to those patients with other

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malignancies [4], and high microvessel density is negatively prognostic [5]. This suggests that tyrosine kinase inhibitors targeting the VEGF receptors (VEGFR) may be of potential benefit in the treatment of MPM. However, other VEGFR inhibitors, such as sunitinib [6,7] and sorafenib [8] have been studied in MPM, and while occasional objective responses have been observed, these agents have not demonstrated compelling single-agent activity.

Dovitinib [Novartis AG] is a multitargeted oral tyrosine kinase inhibitor which inhibits all three VEGFR at nanomolar concentrations, in addition to platelet-derived growth factor receptor β, KIT, ret and fetal liver tyrosine kinase 3. Further, dovitinib inhibits the fibroblast growth factor receptors (FGFR) 1–3 [9]. At the time of initiation of this trial, agents targeted the FGFR family had not been studied in MPM, and the role of the FGFR pathway in the pathogenesis of MPM had not been extensively evaluated. This trial was designed to evaluate an agent targeting both VEGFR and FGFR, and to perform a preliminary evaluation of the FGFR pathway in MPM tumour specimens.

2. Methods

2.1. Patients

This open-label multi-centre phase II trial [NCT01769547] enrolled adult patients with histologically-proven advanced MPM. Patients had previously received combination chemotherapy with platinum and an antifolate (either raltitrexed or pemetrexed); up to one additional line of systemic therapy, not including agents targeting the VEGF or FGFR pathways, was permitted. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2, adequate hematological, renal and hepatic function and measurable disease according to RECIST 1.1 [10]; for those patients with only pleural rind as measurable disease, the RECIST criteria modified for MPM were used [11]. Provision of an archival tumour sample was mandatory. At least 4 weeks had to have elapsed from any prior systemic therapy, radiotherapy and major surgery, with recovery from any related toxicities.

Exclusion criteria included a pulmonary embolism or deep venous thrombosis within 6 months, clinically significant bleeding within three months, significant proteinuria, use of antiplatelet agents or requiring anticoagulation with warfarin (low molecular weight heparin was permitted), significant cardiac dysfunction or arrhythmia, known infection with hepatitis B or C or human immunodeficiency virus, and a prior invasive malignancy within 3 years.

This trial was reviewed and approved by the research ethics boards of the participating institutions and all patients provided written informed consent. The study was conducted in accordance with Good Clinical Practice guidelines. Registration was performed centrally through the Ontario Clinical Oncology Group Coordinating and Methods Center located in Hamilton, Ontario.

2.2. Pre-treatment and on-treatment evaluations

Prior to initiation of therapy, a baseline physical examination was performed, as were routine hematology and biochemistry, thyroid function testing, pulmonary function tests, and computed tomography (CT) scanning of the chest and other sites as required to document extent of disease.

Patients were assessed by the investigator on day 1 and 8 of cycle 1, then on day 1 of every subsequent cycle. Blood pressure was recorded weekly for the first cycle, then on day 1 of subsequent cycles. Hematology and biochemistry were repeated on day 8 of cycle 1, and then on day 1 of every subsequent cycle; thyroid function tests and pulmonary function tests were repeated every second cycle. Toxicity was assessed using the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03 [Bethesda, MD]. Response was assessed every 2 cycles.

2.3. Treatment and study conduct

Patients received dovitinib at the standard intermittent dosing schedule of 500 mg daily orally for five days followed by a 2-day rest [12,13]. For the purposes of this study, a cycle was 28 days. Treatment was continued in the absence of disease progression, unacceptable toxicity or patient request to withdraw. Up to two dose reductions (to 400 mg and then 300 mg daily for 5 days out of 7) for toxicity were allowed. Generally, for grade 2 toxicity treatment was held until resolution to $\leq$ grade 1, and then resumed at the current dose level. For grade 3 toxicity, treatment was held until resolution to $\leq$ grade 1, and then resumed at one dose level lower. Treatment was permanently discontinued for grade 4 toxicity.

2.4. Correlative studies—imaging

Diffusion weighted magnetic resonance imaging (MRI) of the pleura was obtained within 15 days prior to initiation of therapy, and on day 15 of cycle 1. MRI was performed on 1.5 T machines in supine position using body array coils. Sequences included a coronal T2 weighted sequence with coverage of the entire chest, axial T1 sequences (in phase, out of phase, water only and fat only), axial echo planar fast spin echo sequence (HASTE [half-Fourier acquisition single-shot turbo spin-echo]), axial and coronal 3D VIBE (volumetric interpolated breath-hold examination) T1 weighted sequences pre and post gadolinium administration, sagittal 3D VIBE post gadolinium, and single-shot echo-planar imaging (EPI) sequences in axial plane for diffusion weighted imaging, with b values of 0, 500, 800, and 1000 s/mm^2.

MRIs were reviewed by two chest radiologists. Modified RECIST criteria for mesothelioma were used to assess the MRIs. Mean apparent diffusion coefficient (ADC) values were calculated on each study on ADC maps using three regions of interest (ROI) of same size. The ROIs were placed within the solid tumour tissue avoiding areas of necrosis and tumour lung interface in correlation with contrast enhanced sequences.

2.5. Correlative studies—plasma

Samples for correlative studies were obtained at baseline, day 8 of cycle 1, and on day 1 of cycles 2 and 3. Plasma samples were analyzed retrospectively in a blinded fashion, using commercially available ELISAs. For all ELISA tests, with the exception of FGF-23, and sVEGFR3, human specific Quantikine ELISA kits (R&D Systems, Minneapolis MN) were used according to manufacturer's directions. For sVEGFR3, the human sVEGFR3 antibody Duoset (Cat. DY349, R&D Systems, Minneapolis MN) was used to generate a sandwich ELISA according to the manufacturer's directions. Similarly for FGF-23, the human FGF-23 Duoset (Cat. DY2604, R&D Systems, Minneapolis MN) was used to generate a sandwich ELISA according to the manufacturer's directions. Plasma samples were assessed in duplicate, and protein concentration determined by comparison to internally generated standard curves using recombinant protein for each specific ELISA. Patients with levels below the threshold of assay sensitivity were assigned a value equal to 50% of the lower level of detection for statistical analyses.

2.6. Correlative studies—tissue

Archival tumour tissue was collected at enrolment from all patients. Using a commercially available kit (Vysis LSI FGFR1 Spec-