An Open-Label, Multicenter, Randomized, Phase II Study of Pazopanib in Combination with Pemetrexed in First-Line Treatment of Patients with Advanced-Stage Non–Small-Cell Lung Cancer

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Introduction: This randomized open-label phase II study evaluated the efficacy, safety, and tolerability of pazopanib in combination with pemetrexed compared with the standard cisplatin/pemetrexed doublet in patients with previously untreated, advanced, nonsquamous non–small-cell lung cancer.

Methods: Patients were randomized (2:1 ratio) to receive pemetrexed 500 mg/m^2 intravenously once every 3 weeks plus either oral pazopanib 800 mg daily or cisplatin 75 mg/m^2 intravenously once every 3 weeks up to six cycles. All patients received folic acid, vitamin B12, and steroid prophylaxis. The primary endpoint was progression-free survival (PFS).

Results: The study was terminated after 106 of 150 patients were randomized due to a higher incidence of adverse events leading to withdrawal from the study and severe and fatal adverse events in the pazopanib/pemetrexed arm than in the cisplatin/pemetrexed arm. At the time enrolment was discontinued, there were three fatal adverse events in the pazopanib/pemetrexed arm, including ileus, tumor embolism, and bronchopneumonia/sepsis. Treatment with pazopanib/pemetrexed was discontinued resulting in more PFS data censored for patients in the pazopanib/pemetrexed arm than those in the cisplatin/pemetrexed arm. There was no statistically significant difference between the pazopanib/pemetrexed and cisplatin/pemetrexed arms for PFS (median PFS, 25.0 versus 22.9 weeks, respectively; hazard ratio = 0.75; 95% confidence interval, 0.43%–1.28%; p = 0.26) or objective response rate (23% versus 34%, respectively; 95% confidence interval, –30.6% to 7.2%; p = 0.21).

Conclusion: The combination of pazopanib/pemetrexed in first-line treatment of non–small-cell lung cancer showed some antitumor activity but had unacceptable levels of toxicity.

Key Words: Non–small-cell lung cancer, Pazopanib, Pemetrexed, Cisplatin.

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The role of chemotherapy in the treatment of advanced non–small-cell lung cancer (NSCLC) remains mainly palliative, although platinum-based doublet chemotherapy has been proven to significantly improve survival, disease-related symptoms, and quality of life.[1,2] In this context, the addition of cisplatin to a single cytotoxic agent confers an undeniable but moderate benefit for chemotherapy-naive patients with inoperable NSCLC in randomized studies.[3,4] Thus, the trade-off between activity and chemotherapy-related side effects must always be adequately considered in the individual patient.

Few randomized trials have directly compared platinum-based regimens with nonplatinum combinations, but they have generally demonstrated comparable response rates and median survival times.[5–9] Although platinum-free doublets including third-generation agents have been proven to be equally active,[10] clinicians do not commonly use these regimens in daily clinical practice unless platinum agents are contraindicated. The addition of an antiangiogenic monoclonal antibody to a standard cytotoxic doublet provides an additional benefit in terms of disease control[11,12] and overall survival (OS)[12] in selected patients with metastatic NSCLC.

Efforts to identify drugs that inhibit key pathways involved in the pathogenesis of cancer, such as angiogenesis, have also led to the development of multitargeted tyrosine kinase inhibitors (TKI) in the last decade. Pazopanib is a TKI of the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, and stem cell growth factor receptor (c-KIT), and it is approved for the treatment of patients with advanced renal cell carcinoma[13] and advanced soft-tissue sarcoma who have received prior chemotherapy.[14] Pazopanib has demonstrated activity in NSCLC, with 86% of patients with early-stage NSCLC who participated in a preoperative study experiencing volumetric reduction of their tumor after a median duration of 16 days treatment with single-agent pazopanib and with a modest toxicity profile.[15]

Pemetrexed is one of the most active cytotoxic agents used for nonsquamous NSCLC and is a potent inhibitor of thymidylate synthase[16,17] and other folate-dependent enzymes, including dihydrofolate reductase and glycinamide ribonucleotide formyl transferase.[18] Pemetrexed currently has regulatory approval in combination with cisplatin for first-line treatment of malignant pleural mesothelioma[19] and nonsquamous NSCLC[20] and as a single agent for second-line[21] and maintenance treatment.[22–24]

Theoretically in NSCLC, the combination of pazopanib and pemetrexed had the premise for clinically meaningful therapeutic activity coupled with a safe nonoverlapping toxicity profile, potentially better than platinum-based chemotherapy, based on the toxicity profile of each individual agent. A phase Ib study of the combination in patients with solid tumors identified a maximum tolerated dose of pazopanib 800 mg plus pemetrexed 500 mg/m^2.[25] To further explore the activity and the toxicity of this doublet, a randomized, multicenter phase II study was conducted in first-line patients with advanced nonsquamous NSCLC to compare the combination of pazopanib and pemetrexed versus cisplatin and pemetrexed.

PATIENTS AND METHODS

Patient Selection

Chemotherapy-naive patients with histologically or cytologically proven predominantly nonsquamous cell stage IIIB wet (with confirmed malignant pleural effusion) or stage IV NSCLC according to the 6th edition of Tumor, Node, Metastasis classification,[26] at least 18 years of age, with an Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease as defined by the Response Evaluation Criteria in Solid Tumors 1.0,[27] and a predicted life expectancy of at least 12 weeks were eligible. Prior surgery and/or localized irradiation for NSCLC were permitted at a minimum of 4 weeks before study entry. Patients with previously treated, clinically stable, central nervous system metastases were eligible.

Patients were required to have adequate bone marrow, hepatic, and renal function. Exclusion criteria included poorly controlled hypertension; history of cerebrovascular accident, including transient ischemic attack, pulmonary embolism, or untreated deep venous thrombosis within the past 6 months; recent hemoptysis; and known endobronchial lesions.

This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by each participating institution's independent ethics committee. All patients provided written informed consent before any study procedures were performed.

Study Design and Treatment

Eligible patients were randomly assigned (2:1 ratio) to receive either (1) pemetrexed 500 mg/m^2 intravenously (IV) once every 3 weeks for a maximum of six cycles plus oral pazopanib (Votrient; GlaxoSmithKline, Research Triangle Park, NC) 800 mg once daily until completion of the combination treatment and then as pazopanib monotherapy at 800 mg once daily (until disease progression, unacceptable toxicities, or death) or (2) pemetrexed 500 mg/m^2 IV plus cisplatin 75 mg/m^2 IV once every 3 weeks for a maximum of six cycles. Patients were randomized in a 2:1 ratio to obtain sufficient data on the tolerability profile of the pazopanib/pemetrexed combination. Patients on both arms received standard premedication for pemetrexed including dexamethasone (or equivalent corticosteroid), folic acid, and vitamin B12. Patients on the pemetrexed/cisplatin combination were allowed to receive single-agent pazopanib at the time of progression.

Dose modification guidelines for adverse events were prespecified. Cycle delays for pemetrexed or pemetrexed/cisplatin or interruption of pazopanib treatment for up to 14 days were permitted for recovery from adverse events. Concomitant supportive therapies, such as erythropoiesis-stimulating agents or granulocyte colony-stimulating factors, were allowed according to the American Society of Clinical Oncology guidelines.[28]

A Safety Review Committee (SRC), independent of the study team, was established to monitor aggregated safety and efficacy data for each treatment arm on a monthly basis during the conduct of the study. Data reviews began after the first 10 patients in the study had completed the first cycle of treatment. The data reviewed by the SRC included all deaths (disease-related and fatal serious adverse events), serious adverse events, adverse events, study treatment discontinuations, and laboratory investigations (including a targeted review of hematologic toxicity). The SRC was guided by the following criteria in recommending consideration of a study modification or study cessation: "Sufficient evidence to suggest that the true risk of adverse outcomes (e.g., pulmonary hemorrhage, hepatotoxicity, or other adverse events) among patients in the test arm is in excess of that among control