Editorial

Targeting the tumor vascular supply with vascular disrupting agents

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J Thorac Dis 2010; 2: 192-193. DOI: 10.3978/j.issn.2072-1439.2010.11.1

Historically the role of tumor histology in the selection of treatment for lung cancer was limited to differentiation between small cell lung cancer and non-small cell lung cancer (NSCLC). More recently, the importance of tumor histology in the selection of appropriate treatment for patients with advanced stage NSCLC has been elucidated. In a randomized phase II trial of carboplatin and paclitaxel alone or with low- or high-dose bevacizumab, an increased risk of grade ≥ 3 pulmonary haemorrhage was seen in patients with squamous histology (1). As a result, these findings led to the exclusion of patients with squamous histology from phase III trials of bevacizumab in advanced stage NSCLC (2, 3). In addition to its role in reducing a specific adverse event, histological subtypes are also associated with efficacy with recent data indicating pemetrexed combined with cisplatin being more effective in patients with nonsquamous than squamous cell histology (4). Poorer survival has been reported in squamous cell histology in both treatment arms of a phase III study of chemotherapy with or without sorafenib (5) and also in patients receiving chemotherapy combined with motesanib (6).

Tumor vascular supply is a major target in anti-cancer treatment and intense research efforts has resulted in a range of agents approved for clinical use. Vascular targeting strategies can be classified into several approaches including an antiangiogenic approach by targeting vascular endothelial growth factor (VEGF) and its receptors through monoclonal antibodies (bevacizumab) and tyrosine kinase inhibitors (vandetanib, sorafenib). This approach inhibits endothelial proliferation and migration, targeting new blood vessel formation of smaller, solid tumors with a major effect on the periphery of the tumor. A second method is the vascular disrupting approach. Vascular disrupting agents (VDAs) act primarily on endothelial cells and pericytes of established tumor vasculature, resulting in blood vessel occlusion, tumor ischemia and necrosis with a major effect on the central part of the tumor (7, 8). The VDAs currently in clinical development include vadimezan (ASA404), plinabulin (NPI-2358) and combretastatin A4 phosphate (CA4P). ASA404 (5,6-dimethylxanthenone-4-acetic acid or DMXAA) is a small-molecule, flavonoid tumor-vascular disrupting agent. The major mode of action of ASA404 antitumor activity is to induce the synthesis of tumor necrosis factor (TNF)-alpha. In addition, ASA404 can induce vascular endothelial cell apoptosis in tumors independently of TNF-alpha induction (9).

In this issue of the Journal of Thoracic Disease, McKeage and Jameson report on a retrospective analysis of pooled data from phase II studies of ASA404 to compare safety and efficacy between squamous and non-squamous NSCLC patients (10). Data from untreated patients with advanced stage NSCLC who were randomized to receive up to carboplatin (C) and paclitaxel (P) alone or

No potential conflict of interest.

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Submitted Nov 4, 2010. Accepted for publication Nov 6, 2010.
Available at www.jthoracdis.com

ISSN: 2072-1439

with ASA404 (1200 mg/m^2) (11), or enrolled in an extension study to receive CP and ASA404 (1800 mg/m^2) (12), were pooled by histology and by treatment, with aggregation of the two ASA404 doses.

Although the study was not powered for a statistical comparison of outcomes, a numerically higher response rate, time to progression (TTP) and median survival was seen in patients with both squamous and nonsquamous NSCLC treated with chemotherapy and ASA404 compared with those receiving chemotherapy alone. In the squamous patients, the response rate was 14.3% for the chemotherapy alone and 40% for chemotherapy plus ASA404, whilst in non-squamous patients the rates were 25% and 31.7%, respectively. The TTP was 1.6 months for CP alone and 5.6 months for CP plus ASA404 for squamous patients and 4.8 months and 5.5 months, respectively, for nonsquamous patients. In patients with squamous histology, the median survival was 10.2 months and 5.5 months for CP with and without ASA404, respectively, and 14.9 months and 11months, respectively in nonsquamous patients. Overall, the addition of ASA404 to CP was well tolerated in both squamous and nonsquamous patients, with no evidence of hemoptysis in either group. No biomarker analyses were reported.

Although this pooled analysis showed favourable efficacy and toxicity results a randomised phase III trial of chemotherapy with or without ASA404 in both squamous and nonsquamous NSCLC patients was halted as interim data analysis showed futility (13), once again highlighting the importance conducting large prospective randomized studies to confirm results of smaller phase II studies. Studies of other VDAs are currently being conducted. Presently there are no proven biomarkers for selecting patients with NSCLC who would benefit from VDAs. An analysis of biomarkers from the recently halted first line study may help identify a subset of patients who may benefit from chemotherapy in combination with ASA404. Such biomarker data may facilitate the development of ASA404 in future studies.

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