Perspective

Carboplatin, paclitaxel and sorafenib in advanced melanoma – what have we learned?

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Sorafenib is a small orally available multikinase inhibitor which is approved for the treatment of advanced renal cancer and hepatocellular carcinoma and is one of the first agents in molecular targeted therapy that was brought into clinical trials for metastatic melanoma patients. It blocks tumor proliferation by targeting the vascular endothelial growth factor receptors, platelet-derived growth factor receptors, RAF1, BRAF and probably other receptors involved in signal transduction in tumor cells (1). It is not exactly understood which targets of the above are the most relevant ones in the therapy of advanced melanoma.

In a double blind randomized phase II study sorafenib was investigated in combination with dacarbazine versus dacarbazine alone. In a dose of 400 mg twice daily in 101 patients (2) there was a sign for improved progression free survival (PFS) and an improved response rate. However the differences were not significant.

Hauschild *et al*. conducted a randomized placebo-controlled phase III clinical trial (PRISM) comparing polychemotherapy with carboplatin and paclitaxel alone versus in combination with sorafenib in a patient population of 270 advanced melanoma patients in the second line setting (3). There was a response rate of 11% or 12% for the sorafenib group with very similar progression free survival of approximately 4.5 months. In a very recent issue of the *Journal of Clinical Oncology*, Flaherty *et al*. published the results of a phase III study with similar design as the PRISM in chemotherapy-naïve metastatic melanoma patients (4). In this study the combination carboplatin, paclitaxel plus placebo was compared to the two chemotherapeutic drugs in combination with sorafenib. There was a response rate of around 20% in both arms with a very similar progression free survival of 4.2 months for carboplatin-paclitaxel and 4.9 months for carboplatin-paclitaxel and sorafenib with no impact of overall survival.

There are several interesting conclusions that can be drawn from this data:

(I) The response rate and the progression free survival is very similar for the aggressive polychemotherapy both in first and second line setting (3,4);

(II) The addition of sorafenib in unselected patient populations does not improve the response, nor the progression free survival.

There are some indications that sorafenib might provide a benefit in certain subpopulations of melanoma patients, such as in patients with high LDH levels or special melanoma subtypes, such as sinonasal or uveal melanomas. However there is currently no accepted biomarker which allows us to identify the patients that are more likely to respond to sorafenib.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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