More effective agents still needed for progressive radioiodine-refractory differentiated thyroid cancer

Dear Editors

A letter (Pitoia 2014) which doubted the conclusions of our meta-analysis (Shen et al. 2014) has been published recently, in which the author wondered whether 70% of partial response (PR) plus stabilization of disease (SD) would be considered as a modest response to treatment with sorafenib in patients with radioiodine-refractory differentiated thyroid cancer (DTC). Here, we make some clarifications:

Firstly, ‘70%’ may not really reflect the effect of sorafenib. According to the results of the DECISION trial (Brose et al. 2013), the progression-free survival (PFS) reached 5.8 months and SD 33% in the placebo arm. All the data of SDs obtained in the seven clinical trials of the meta-analysis were assessed within 6 months, which is too short compared with the 5.8 months of PFS. Moreover, in the DECISION trial, the primary endpoint was PFS, and the secondary endpoints included overall survival (OS), response rate (complete response (CR) + PR), and safety; however, SD was not used as an endpoint. We think that the pooled SD in the meta-analysis which reached 52% may not accurately represent the response of sorafenib in the treatment of radioiodine-refractory DTC. Therefore, SD cannot accurately represent the response of sorafenib. Only CR and PR may represent the response rate. As far as we can discern, OS may be the best evaluation index for the treatment response in radioiodine-refractory DTC patients. Unfortunately, no data that compares the differences between sorafenib arm and placebo or other agents has been reported. In the DECISION trial, median OS has not yet been reached in either arm.

Secondly, we made the point that the pooled PR in our meta-analysis was 22% (which could result in an overestimation of the effects, because all of the seven clinical trials lacked randomization and blinding). Recently, a retrospective study evaluating tyrosine kinase inhibitors (TKIs) therapy outside of clinical trials in five French oncology centers has reported that among 39 DTC patients treated with sorafenib, the PR rate was 15% (Massicotte et al. 2014); in the DECISION trial (Brose et al. 2013), it was 12.2%. However, as mentioned in the discussion of our meta-analysis, lots of new agents have been studied to evaluate their efficacy in the treatment of radioiodine-refractory DTC. Among them, pazopanib (Bible et al. 2010) reached a confirmed PR in 18 of the 37 patients (49%) and selumetinib (Ho et al. 2013), a MAPK kinase (MEK) 1 and MEK 2 inhibitor, increased the uptake of iodine-124 in 12 out of 20 patients (60%). It seems that RECIST criteria do not properly evaluate all the real benefits of the new targeted agents in solid tumors including DTC, so there is an ongoing discussion about the best criteria for the evaluation of the antitumor efficacy of targeted therapies. However, considering the absence of alternative validated criteria and the increasing evidence of functional imaging as a predictive evaluation modality (Carr et al. 2010), RECIST continues to be the mainstay of response evaluation for molecular targeted therapies.

Thirdly, although mostly graded as 1 or 2, the high incidence of adverse effects associated with sorafenib may affect patient quality of life. In our meta-analysis, the pooled incidence of dose reductions due to toxicity of sorafenib was 62% and treatment withdrawals were also reported in the eligible trials. A case (Bellesoeur et al. 2014) has currently been reported that since sorafenib exposure had decreased over the time, its doses were increased up to 1600 mg bid, in order to maintain clinical activity and to restore active plasma concentration. Although the toxicity was mild and manageable, the patient eventually experienced grade 3 proteinuria leading to treatment discontinuation.

Clinically, even in progressive or metastatic radioiodine-refractory DTC (such as the most common lung metastases), many patients will be relatively asymptomatic and do not complain of great discomfort under thyroid-stimulating hormone (TSH) suppression therapy. The quality of life is not significantly affected. However, with molecular targeted therapies, such as the administration of sorafenib, the majority of patients will suffer different degrees of adverse effects. In addition, four of the seven clinical trials in our meta-analysis reported a dose...
adjustment of thyroid hormone requirements due to change in TSH levels (mostly increased). Targeted therapy cannot completely eradicate tumor cells and the drug would potentially be administered for the rest of the patient’s life. With one or more withdrawals of sorafenib and dose reduction, the risk of disease progression may increase. All of these points discussed above may affect the quality of life in DTC patients. Moreover, some patients may be intrinsically resistant to TKIs or may develop resistance during the targeted therapy (Gauthier & Ho 2013). Above all, those points discussed above have to be weighed against application in patients with radioiodine-refractory DTC and the requirements of individualized treatment in carefully selected patients.

Finally, our meta-analysis did not deny the efficacy of sorafenib in the treatment of radioiodine-refractory DTC patients. Considering its response rate (CR+PR), adverse effects, drug tolerability, and potential influence on the quality of life in DTC patients, we highlighted that the utility of sorafenib in the treatment of radioiodine-refractory DTC should be cautiously optimistic, and more effective agents with reduced toxicity and cost are still required.

In addition, as far as we are concerned, the definition of radioiodine-refractory DTC is vague (including not only radioiodine non-uptake but also non-efficacy despite radioiodine uptake DTC). There are also differences in the concept among radioiodine-refractory DTC, advanced DTC, progressive DTC, and radioiodine non-uptake DTC. It has to be emphasized that not all radioiodine-refractory DTC patients need to be treated with molecular-targeted therapies. Only patients with aggressive, relatively rapidly progressive disease can be considered and molecular-targeted agents such as sorafenib could be an alternative treatment.

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