disclosure

The author has declared no conflicts of interest.

references


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Reply to the letter to the editor ‘Treating breast cancer with trabectedin: a new arsenal’ by L. Malik

We are grateful to Dr Malik for his interesting comments and agree that the findings of this phase II trial are encouraging. Indeed, trabectedin’s efficacy has been repeatedly suggested, through in vitro and in vivo findings, to be related to homologous recombination (HR) repair abnormalities involving ERCC1/5 and BRCA1 [1, 2]. This study was the first to target such a BRCA1/2-mutated population with an HR-directed agent. Certainly, due to the limited patient population, trabectedin activity observed in BRCA-mutated metastatic breast cancer patients should be considered with caution; as clearly mentioned in the study publication.

However, we believe the results of the trial are positive and worthy to be disseminated. The study population consisted of highly pretreated patients (median of 4, but up to 10, previous therapy lines in the metastatic setting), all carrying BRCA1/2 germline mutation, of whom 52.5% had triple-negative breast cancer. Tumor response rate (RR) by RECIST was chosen as primary end point to have a proof of concept of trabectedin activity in this rare population, as well as to have a dichotomous variable to perform a futility analysis. Progression-free survival (PFS) was a prospectively defined secondary end point. Both were assessed by an independent review board.

As per protocol, only treated patients with measurable disease were assessable for efficacy. Therefore, of the 40 recruited patients, 2 received no study treatment and 3 did not have target lesions by independent radiological review (although they did by investigator assessment). Consequently, and as indicated in the publication, the remaining 35 were assessable for efficacy. Although the approved dose for single-agent trabectedin in sarcoma is 1.5 mg/m² as a 24-h infusion every 3 weeks, the dose used in this trial (1.3 mg/m² as 3-h infusion every 3 weeks) appeared to be similarly active in prior trials with other indications [3] and more convenient for the patients and is widely used in practice. Also per protocol, granulocyte colony-stimulating factor was not allowed as primary prophylaxis; nine patients (22.5%) received it as secondary prophylaxis, according to the investigators’ criteria.

The safety profile was acceptable, with no cumulative toxicities. Creatine phosphokinase (CPK) elevation, which occurred in 26% of the patients, was reversible and similar to that observed in the pool of phase II trials with trabectedin monotherapy (23.2%) [4]. None of these episodes of CPK elevation had clinical manifestations. This parameter was not recorded in the study mentioned by Dr Malik for the comparison of CPK increase incidences [5].

The very low recruitment rate (40 patients in 4 years), was due to the rarity of already identified BRCA1/2-mutated breast cancer patients with metastatic disease; at that time, BRCA1/2 testing criteria were much narrower than at the present time. Overall, we agree with Dr Malik that, in this heavily pretreated population that still has an urgent and unmet medical need, a RR of 17% and a PFS of 3.9 months together with an acceptable benefit/risk ratio represent a step forward and deserve further evaluation.

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