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Trabectedin in ovarian cancer: could we expect more?

Treatment of recurrent ovarian cancer is still a major challenge. As for other tumor types in which cure cannot be achieved, the main criteria for selecting therapies are antitumor activity, for which progression-free survival (PFS) 'might be' an acceptable end point, as concluded in the FDA/ASCO/AACR workshop of 2006 [1], and safety, which also depends on the extent of disease and extent of prior treatment with related persisting toxic effects.

Rechallenge with platinum is common practice in recurrent disease and its efficacy is correlated with interval from last platinum administration to subsequent relapse, a time interval defined as platinum-free interval (PFI). In a broadly accepted classification, a PFI of <6 months indicates a platinum-resistant disease, a PFI of 6–12 months indicates a partially platinum sensitive and a PFI of >12 months indicates a platinum-sensitive disease [2].

The DNA-binding agent trabectedin (T) in combination with pegylated liposomal doxorubicin (PLD) has been approved in Europe in 2009 for the treatment of patients with relapsed platinum-sensitive ovarian cancer. The approval is based on the results of the phase III OVA301 study in which 672 patients, relapsing after a first-line platinum-based therapy, were randomized to T/PLD or PLD alone [3]. In comparison to PLD, the combination of T/PLD significantly prolonged median PFS [7.3 versus 5.8 months; hazard ratio (HR) = 0.79, $P = 0.0190$], with possibly even greater activity in platinum-sensitive patients (median PFS: 9.2 versus 7.5 months; HR = 0.73, $P = 0.0170$). There was no difference in overall survival (OS) at the first protocol-specified interim analysis conducted with 300 events (versus 520 required for the final analysis). However, at the updated OS analysis conducted at the request of Regulatory Authorities with an additional year of follow-up, a significant 41% decrease in the risk of death was found in the partially platinum-sensitive subset (HR = 0.59, $P = 0.0015$), with a median OS of 23 versus 17.1 months [4]. The OVA301 study is therefore of relevance because it confirmed in a large subset of 431 platinum-sensitive patients that combination therapy is better than single agent and defined the potential value of a non-platinum-containing combination in this setting [5].

To better understand the effect of T/PLD in prolonging survival in platinum-sensitive patients, a *post hoc* exploratory analysis was carried out with a detailed assessment of the subsequent therapies, in particular modalities of reintroduction of platinum and evaluation of PFI, the results of which are reported in two complementary somewhat overlapping papers in this issue of *Annals of Oncology* [4, 6].

The characteristics of the subsequent treatment were comparable in the two arms, consisting of chemotherapy in ~70% of patients, platinum-based in ~50% [4].

In the T/PLD, the time from randomization to subsequent platinum-based therapy was significantly longer (9.8 versus 7.9 months; HR = 0.64, $P = 0.0167$). Median survival from the initiation of subsequent platinum-based therapy was also longer (13.3 versus 9.8 months; HR = 0.63, $P = 0.0357$) [4]. Differences were larger in those patients who received platinum as first subsequent therapy, with a time to subsequent therapy of 11.5 versus 7.5 months (HR = 0.61, $P = 0.0203$) and a median survival from the initiation of platinum of 18.6 versus 9.9 months (HR = 0.54, $P = 0.0169$) [6].

The retrospective nature of this exploratory analysis and the lack of information on response to subsequent treatments and duration do not allow to draw conclusions on a possible beneficial effect of T on a longer PFI and survival. On the other hand, these results show that after T/PLD a combination with platinum could be still effective and confirm that T/PLD is a suitable option for platinum-sensitive patients who could be still suffering from residual platinum/taxanes side-effects.

In the recently published Calypso study, carried out in 976 patients with late platinum-sensitive relapsed ovarian cancer, the combination of PLD and carboplatin (CD) was shown to be superior in PFS (median PFS 11.3 versus 9.4 months; HR = 0.82, $P = 0.005$) to standard carboplatin and paclitaxel (CP), with a more favorable safety profile [7]. Based on these results, CD was defined as more effective less toxic alternative to current standard CP in platinum-sensitive patients.

In view of the available information, which is the best alternative to standard CP in recurrent platinum-sensitive disease? Besides theoretical considerations on a potential effect of T in prolonging PFI and the correlation between PFI and reversal of platinum resistance, the main issue is the value of PFS as surrogate of OS in the assessment of new regimens in recurrent disease [5].

The role of T/PLD and CD as second-line therapy in patients progressing within 6–12 months of last platinum will be conclusively defined in the INOVATYON study, a phase III international randomized study coordinated by MaNGO (Mario Negri Gynecologic Oncology Group), which will be activated within the end of 2010 in many European countries. The study has a planned sample size of 588 patients to demonstrate a statistically and clinically significant difference in OS in favor of T/PLD, with a decrease of the risk of death of at

least 17.4%. This study therefore will provide a definitive answer not only on the role of T and of a non-platinum-containing combination but also it will evaluate the effect of a longer PFI on response to subsequent platinum and OS.

Could we expect more from T in ovarian cancer besides being part of an effective second-line therapy? So far, the main interest in T resided in its known mechanisms of action, with DNA binding in the minor groove and interaction with DNA repair proteins; cells deficient in Homologous Recombination were shown to be much more sensitive to T, similar to what is observed with platinum compounds, while cells deficient in nucleotide excision repair were shown to be less sensitive. From all the studies carried out so far on the molecular pharmacology of T, it seems clear, however, that the drug has more than one mechanism of action.

T has also the ability to modulate transcription of a limited subset of genes, a mechanism that has been clarified in some sarcomas, with a well-defined deregulation of expression of some specific transcription factors, but which is still to be elucidated for other neoplasms, for which alterations in the regulation of transcription seems to be very likely, but not precisely defined, like ovarian cancer [8].

T probably modulates transcription also in some normal cells. In this respect, there is a growing evidence that T has a high specificity for macrophages that are very sensitive to it.

Following treatment with T, tumor-associated macrophages appeared to be reduced in number and modified their production of cytokines, chemokines and growth factors [9, 10]. It seems plausible that these effects are very important *in vivo* and may explain some of the clinical observations. For example, if part of the antitumor activity of T is due to the inhibition of production of factors that promote angiogenesis, tumor growth and metastatisation, it might be expected that the drug does not necessarily cause a fast tumor shrinkage but that the response is obtained after several courses, as it has been observed in some ovarian cancer and sarcoma patients. Similar results have been reported in a myxoid liposarcoma murine xenograft [10, 11].

An interesting unpublished observation by the laboratories of the Department of Oncology at Mario Negri Institute is that an ovarian cancer cell line made resistant to T after prolonged drug exposure *in vitro* was no longer resistant when transplanted in mice, suggesting that the antitumor properties of the drug are not only due to a direct effect on cancer cells but are also possibly mediated by host effects (e.g. macrophages).

A large body of data indicates that inflammation is relevant for ovarian cancer growth and progression and we can speculate that the T ability to modulate inflammatory and angiogenic factors may play a therapeutic role. If this is the case, an earlier use of T in the treatment of patients with ovarian cancer could provide the best effects. As shown in preclinical models, the combination of T and cisplatin produced cures of ovarian cancer xenografts not curable with any other regimens [12]. This is the reason why efforts should be made to evaluate if the combination of T with platinum complexes is clinically feasible. In addition, the observed inhibitory effect on proangiogenic factors invite to speculate that T could be successfully combined with antiangiogenic therapies, a hypothesis that should be urgently tested at preclinical and clinical level.

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