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Overview

Trabectedin in Ovarian Cancer: is it now a Standard of Care?

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Abstract

In patients with recurrent ovarian cancer, the choice of second-line therapy is complex. Several factors have to be considered, such as platinum-free interval (PFI), residual toxicity from the previous treatments, BRCA1/2 gene mutation status. Trebectedin is a minor groove DNA binder derived from a marine organism that has shown efficacy in different settings in ovarian cancer therapy. It has been approved in the treatment of partially platinum sensitive (PPS) (PFI between 6 and 12 months) relapsed ovarian cancer according to the statistically significant progression-free survival (7.3 versus 5.8 months) and overall survival (22.2 versus 18.9 months) benefit compared with single-agent pegylated liposomal doxorubicin (PLD) in the OVA 301 phase III trial. This drug has been shown to prolong the time to first subsequent treatment and improve the efficacy of further platinum-based chemotherapy. The role of trabectedin/PLD followed by platinum combination compared with the reverse sequence in PPS is actually in evaluation in the INOVATYON phase III study, which will clarify the best sequence to be adopted in this setting. Trabectedin has been shown to be active in patient carriers of BRCA mutations, probably for its mechanism of action directly affecting DNA and it is actually tested as a single agent in some phase III trials in BRCA mutated and BRCA*ness* ovarian cancer patients. Trabectedin is also active on the immune system. There is, therefore, the rational for new trials of a combination with immune checkpoint inhibitors.

Key words: BRCA; ovarian cancer; partial platinum sensitive relapse; trabectedin

Statement of Search Strategies Used and Sources of Information

Scientific papers and the literature database PUBMED were used for this overview.

Introduction

Ovarian cancer represents 30% of female genital malignant tumours and generally affects women over 65 years of age [1,2]. About 75% of women come to diagnosis with advanced cancer (FIGO stage III or IV) in which the 5 year survival is 15–20% [3]. Cytoreductive surgery followed by a platinum-based chemotherapy ± bevacizumab is the standard of care in advanced stage [4–10]. However, although most cases achieve a positive response to first-line treatment, 70–80% of patients with advanced disease will develop a recurrence within the first 2 years and require one or more subsequent lines of treatment, which aims to prolong the overall survival and improve quality of life [3,11]. The choice of second or further lines of therapy depends on the interval between the end of treatment with platinum and disease recurrence, defined as the platinum-free interval (PFI). The PFI is actually the major predictive factor that influences subsequent platinum responses [12–14]. In fact, in platinum-sensitive patients (disease recurrence at ≥12

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months after initial therapy), a second-line treatment with platinum gives a response rate of 30–60% [15,16], with a further advantage from the addition of bevacizumab (OCEANS trial) [17]; however, this benefit tends to decrease in partially platinum-sensitive (PPS) patients (disease recurrence at 6–12 months) and in platinum refractory or resistant patients (disease recurrence during the first line or within 1–6 months) [15,16]. PPS patients represent a grey area in terms of platinum resistance/responsiveness. The response rates after platinum re-treatment range between 27% and 33% compared with non-platinum drugs. Therefore, the optimal management of PPS recurrent ovarian cancer patients is still unclear. In addition to re-treatment with a platinum-based regimen, single-agent chemotherapy, such as pegylated liposomal doxorubicin (PLD), topotecan or gemcitabine, is an option, showing response rates of 16–40% [18–27]. Recently, trabectedin has received great interest due to a phase III study that showed an overall response rate of 39.4% in recurrent ovarian cancer when combined with PLD. Furthermore, the trabectedin/PLD combination showed a median prolongation of the PFI of 4 months in PPS relapsed ovarian cancers and this may improve the response to the subsequent reintroduction of platinum [28,29]. Also of interest is the role of trabectedin in BRCA-mutated patients who generally presented as high-grade serous tumours characterised by genomic instability. In particular, trabectedin showed a better response in terms of overall response rate (ORR), progression-free survival (PFS) and overall survival in a BRCA1-mutated subgroup, probably because this genetic mutation was associated with the inefficiency of the DNA repair mechanism of homologous recombination repair (HRR) [30].

Mechanism of Action of Trabectedin

Trabectedin is a tetra-hydro isoquinoline alkaloid, originally isolated from the marine tunicate *Ecteinascidia turbinata*, and is produced synthetically [31].

Several scientific studies report the complexity of the mechanisms of action of this drug [32,33]. From the trabectedin structure derive two main effects: the development of a covalent link with DNA, at the N2-guanine of the minor DNA groove, enabling trabectedin interaction with DNA and the capacity to stick-out DNA helix, making it available to tie with DNA-binding molecules, such as transcriptional factors and DNA repair proteins. The development of a link between trabectedin and DNA groove has another relevant effect: a portion of the helix becomes recognisable by the nucleotide excision repair (NER) system, thus determining an accumulation of DNA–trabectedin–protein repair complexes. The latter phenomenon, in turn, leads to three main effects: the formation of double-strand DNA breaks, blocking the cell cycle in G2-M phase and the induction of p53-independent apoptosis [33,34].

According to these findings, to achieve efficient trabectedin cytotoxicity, a functional NER system is required. Chinese hamster and human ovarian cell lines deficient in NER system activity genes (e.g. xeroderma pigmentosum, complementation group A, B, D, F and G) and in the gene of excision repair cross-complementation (ERCC1), are resistant to trabectedin [35,36]. On the other hand, trabectedin is more effective in cells with deficient HRR [37], such as those with BRCA gene mutation or the BRCA*ness* phenotype, which are about 100 times more sensitive to the drug.

In vitro studies have shown that the exposure of proliferating mammalian cells to trabectedin is associated with a rapid formation of DNA lethal double-strand breaks and the presence of unrepaired double-strand breaks is persistent when the loss of HRR is present, even if the trabectedin is removed [38]. So the cells with HRR deficiency, like the BRCA1/2 mutation, are more sensitive to trabectedin due to the persistence of DNA lesions and the highest formation of replication-dependent double-strand breaks.

In this way, cancer models suggest that the response to trabectedin is better in the presence of an efficient NER system and a deficient HRR, because of their synergic action on the DNA repair [39]. Apart from disrupting DNA function and interfering with transcription regulatory pathways, emerging evidence indicates that trabectedin has other effects. Particularly it reduces the production of some inflammatory mediators in the tumour microenvironment [40] and depletes blood monocytes and tumour-associated macrophages in tumour-bearing mice, but also in tissue biopsies from ovarian cancer.

This effect can be associated with the ability of trabectedin to induce the activation of Caspase 8 downstream of the TNF-related apoptosis-inducing ligand (TRAIL) membrane receptor that is more expressed in monocytes and macrophages [41], which are involved in the tumour microenvironment production of growth factors that promote tumour survival and metastatic phenotype.

It is known that the patients treated with trabectedin have a better response to a subsequent platinum-based therapy; the reason for this response is associated with some alterations that the ovarian cancer cells acquire during treatment. In fact, trabectedin has shown inhibitory activity against the production of inflammatory cytokines, such as interleukin-6 and the tumour-associated macrophages, that normally decrease platinum sensitivity and have a tumour-promoting action [42,43].

Another mechanism is the delay in the cell cycle from G1 to G2 phase, with a consequent G2/M block in cells with a proficient NER system. D'Incalci *et al.* [42] support this observation, showing that cells resistant to trabectedin that are defective in the NER system did not have the G2/M block; so the use of trabectedin could select cells with NER deficiency, which are more sensitive to UV light and to drugs like platinum. Thus, the trabectedin-resistant cells exposed to platinum are more sensitive to the drug because of an increased formation of DNA interstrand crosslinking, which are the critical toxic lesion of platinum.

Excursus of Literature

Trabectedin has shown antitumoral activity in many cancers [44–46]; in ovarian tumours it has been evaluated

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