

Editorial

High-dose chemotherapy for ovarian cancer: Are we ready to go?

"The wise man doesn't give the right answers, he poses the right questions."

– Claude Lévi-Strauss

Sixty to seventy percent of patients with invasive epithelial ovarian cancer have chemotherapy-sensitive tumors. Nevertheless, despite excellent responses most of the tumors eventually recur and the patients die of the disease. Numerous mechanisms have been invoked to explain the emergence of drug resistance, one of them being inadequate dose intensity during the initial treatment resulting in the selection of resistant cell clones. An increase of the dose of chemotherapy is the logical consequence of this observation.

Prior to the 'taxane era' several randomized trials investigating platinum dose intensity failed to demonstrate benefit for moderate increases in chemotherapy dosage without stem cell support [1–7]. The standard regimens in these trials usually contained cisplatin at a dosage of 50 mg/m² or carboplatin at a projected area under the curve (AUC) of 4–6 mg/ml·min. Only the Scottish trial reported that a higher dose of cisplatin (100 mg/m²) yielded an advantage in terms of survival [8]. This study, however, has been criticized for the unexplained poor outcome of the patients in the lower dose arm. Overall, there is still no evidence from randomized trials suggesting that an increase of the dose intensity of cisplatin beyond 25 mg/m²/week or of carboplatin beyond an AUC of 6 mg/ml·min every three weeks is beneficial [9].

At this time, we are not aware of any randomized clinical trial that would provide support for using higher than standard doses of paclitaxel.

The paper by Ledermann et al. in this issue [10] reports on one of the largest series of patients treated with high-dose chemotherapy in ovarian cancer. Most of these patients have received high-dose chemotherapy in phase II studies or outside of a clinical trial. Health agencies seem to be prepared to finance expensive treatments outside the context of clinical research, although they are still reluctant to support the same therapies within randomized clinical trials.

The paper reveals a few weak points that are unavoidable in this type of retrospective study:

- The data come from a registry report; therefore, the selection of patients is heterogeneous, and it is very likely that only patients with a relatively favorable prognosis were selected, as in similar previous studies in breast cancer [11, 12]. Nevertheless, the treatment results in terms of recurrence-free and overall survival are very similar to

those of the recently reported North American registry study [13].

- Clinical data were often unavailable: the extent of residual cancer after surgery or before beginning high-dose therapy was unknown for a relevant proportion of patients. The amount of residual tumor might have an important prognostic value as illustrated by the substantially different outcomes reported by Legros (59% DFS at five years) [14] and Stiff (less than 20% DFS at five years) [15].
- Toxicity data show a considerable percentage of procedure-related deaths (7%). Similar results have been reported by Stiff (11%) [13]; in recent years, however, mortality decreased substantially to 3% with improvements in supportive measures.

This paper clearly demonstrates that high-dose chemotherapy is feasible and reasonably safe in patients with ovarian cancer. The results in terms of survival are comparable to those in chemosensitive recurrences reported by Rose (median progression free survival nine months) using a standard dose paclitaxel/carboplatin regimen [16]. Unfortunately, the current retrospective registry analysis does not allow the definition of subgroups for which high-dose therapy is more effective than conventional therapy.

In the light of the development of high-dose chemotherapy in breast cancer, the authors of this report on the same type of treatment for ovarian cancer are to be commended for avoiding the error of drawing premature conclusions but for embarking on a randomized controlled trial comparing modern conventional chemotherapy with high-dose treatment with autologous stem cell support. Their effort merits the full support of the oncology community.

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