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Title: Progressive epithelial ovarian carcinoma. Prognostic factors and clinical management

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Abstract:

The surgical and cytotoxic treatment of patients with primary epithelial ovarian cancer is standardized according to FIGO (International Federation of Gynaecology and Obstetrics). In contrary, the optimal management of patients with recurrent ovarian cancer (POC: Progressive Ovarian Carcinoma) is presently not settled. Based on the clinical data from a large cohort of POC patients (The CODOVA database), recent treatment strategies have been challenged and new hypotheses generated. The thesis reviews the results from these studies and discusses the clinical application of the results.

It was demonstrated that POC patients with a solitary tumour had increased probability for complete secondary cytoreduction. The selection criteria for an optimal candidate for secondary surgery should be re-evaluated and include the parameters: solitary tumour, tumour size less than 10 cm, favourable performance status, and no prior second-line chemotherapy before surgery. We found that secondary surgical cytoreduction in POC patients has dubious impact on survival. The application of secondary surgery should be based on evidence from randomised trials. Unfortunately, such a trial comparing patients randomised to surgery versus no surgery, and equivalent chemotherapy (Larocson EORTC 55963) has recently been discontinued which limits the probability that level I evidence will ever prevail in this clinical setting.

The optimal cytotoxic regimen in POC patients is presently elucidated in multiple randomised trials. In POC patients with platinum-sensitive disease, the combination of two cytotoxic agents has proven favourable to single-agent therapy (carboplatin) in terms of prolonged survival. Regarding the potential of increased toxicity by combination chemotherapy, we found no evidence of increased neurotoxicity by using a re-treatment regimen of paclitaxel+carboplatin in paclitaxel+platinum pre-treated patients. Which agent that should be combined with carboplatin, and whether the other agent should be administered as combination chemotherapy or sequentially, is presently under evaluation.

In POC patients with platinum-resistant disease, the combination of two agents compared with single-agent treatment has, so far, added nothing but increased toxicity. In a Scandinavian, multi-centre phase I-II study, we found unpredictable toxicity by a sequential regimen of topotecan (iv) and oral etoposide. Moreover, it was found that the therapeutic index of single-agent topotecan might be improved by using a low-dose regimen (1.0 mg/m² days 1-5 every 3 weeks) compared to the full-dose FDA-approved regimen (1.5 mg/m² days 1-5 every 3 weeks). We demonstrated no difference in haematological toxicity between older (\geq 65 years) and younger (< 65 years) patients, and the choice of second-line antineoplastic treatment in patients with POC should thus be based on other parameters than the chronological age. The high response rates reported in recent phase II trials of platinum-based combination chemotherapy in patients with "platinum-resistant" disease challenges the concept of platinum-sensitivity as a treatment guide in patients with POC. Thus,

there is a need to reveal more accurate clinical predictors of the efficacy of the second-line treatment.

We demonstrated that stable disease during second-line chemotherapy of POC is associated with a survival benefit compared to patients with PD. Stabilization of the tumour burden should be considered as a reasonable treatment outcome, because POC is considered as an incurable disease and extension of survival is among the main therapeutic goals. Recently, a new treatment concept, treatment beyond disease progression, has emerged. Conventional oncological practice suggests that if tumour progression occurs during therapy further treatment with the same agent is not indicated. Whether this holds true also for the novel biological agents with minimal toxicity and distinct non-cytotoxic effects remains to be determined.

Contrary to primary ovarian cancer, tumour tissue is rarely available in POC patients outside clinical trials. This fact highlights the utility of serological tumour markers in the clinical management of the disease. We found that tumour marker based response evaluation (CA125) was more accurate than classical imaging-based response evaluation in prognosticating survival in the second-line chemotherapy. CA125-based response criteria should thus be accepted by regulatory authorities in the drug approval process of new agents in the treatment of ovarian cancer. In the individual patient management, CA125-based response criteria should be preferred to imaging-based response criteria in the monitoring of second-line chemotherapy.

We found the serological tumour markers CA125 and CASA, respectively, to be prognostic factors for survival in patients with POC. The tumour marker, CA125, was included in a novel three-covariate prognostic index (The Copenhagen Index) with potential use both in trials and in the individual patient management. The transportability of the Copenhagen Index should be validated in another data set. Preliminary data from a study of the prognostic impact of a panel of serological tumour markers (tetranectin, YKL-40, CA125, CASA) suggest that tetranectin might be a better prognosticator than the other markers. Future studies should reveal if the combination of several serological tumour markers in an index gives added prognostic information. Overall, the findings in the thesis infer an increased confidence in the use of serological tumour markers in the clinical management of patients with POC.