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Alopecia as surrogate marker for chemotherapy response in patients with primary epithelial ovarian cancer: A metaanalysis of four prospective randomised phase III trials with 5114 patients

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Abstract ***Purpose:*** Alopecia is a common side-effect of chemotherapy and affects quality of life of cancer patients. Some patients and physicians believe that alopecia could be a surrogate marker for response to chemotherapy and impact on prognosis. However, this was never been tested in a sufficiently large cohort of ovarian cancer patients.
Patients and methods: We analysed retrospectively the meta-databank of four prospective randomised phase-III-trials with platinum- and taxane-based 1st-line-chemotherapy in patients with advanced epithelial ovarian cancer (EOC) regarding the impact of alopecia overall outcome.
Results: For 4705 (92.0%) of a total of 5114 EOC-patients alopecia was documented. They had received on median six cycle platinum-taxane chemotherapy (range 0–11) with 4186 (89.0%)

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having completed ⩾6 cycles. Worst alopecia grade was 0 in 2.4%, 1 in 2.9% and 2 in 94.7% of the patients. In a univariate analysis, including all patients, grade-0/1 alopecia was associated with significantly lower progression free survival (PFS) and overall survival (OS) compared to grade-2 alopecia. However when assessing only those patients who completed ⩾6 chemotherapy-cycles and hence eliminating the bias of lower total dose of treatment, alopecia failed to retain any significant impact on survival in the multivariate analysis. Merely the time point of alopecia onset was an independent prognostic factor of survival: patients who developed grade-2 alopecia up to cycle 3 had a significantly longer OS compared to patients who experienced alopecia later during therapy (hazard ratio (HR): 1.25; 95% confidence interval (CI): 1.04–1.50).
Conclusions: Within a large EOC-patient cohort with 1st-line platinum- and taxane-based chemotherapy early onset alopecia appears to be significantly associated with a more favourable outcome in those patients who completed ⩾6 chemotherapy cycles. It remains to be elucidated if early onset alopecia is just a surrogate marker for higher sensitivity to chemotherapy or if other biological effects are underlying.

1. Introduction

In the context of an individual's life, a cancer diagnosis is a major event, with an understandable emphasis on survival which patients may deem more important than their quality of life, self body image and sexuality [1]. The desire to prolong survival or even achieve a cure can result in the patient accepting the complications associated with both extensive surgical interventions and the sequelae of systemic therapies [2]. Short- and long-term toxicities like polyneuropathy, fatigue and loss of appetite, tend to be the accepted and are often unavoidable consequences of effective systemic modalities [3]. Alopecia represents a typical example of such a treatment related toxicity. Interestingly, very little is known about mechanisms of apoptosis induced chemotherapy in human hair follicles. Among all chemotherapy induced side-effects, cancer patients have ranked the loss of their hair as the second most severe one [4], often experiencing this as a constant visual reminder of their disease [5,6]. Nevertheless, large surveys in women with breast cancer have demonstrated that only a relatively small proportion of the patients would decline a potentially lifesaving or life-prolonging cytotoxic treatment to avoid alopecia [7,8]. Clinical experience has shown that some patients may tend to perceive alopecia as an indirect evidence of success of their chemotherapy regimen, as it reflects successful targeting of similarly rapid-growing cells i.e. cancer cells, by the toxic chemotherapy agent [9,10]. There are no studies so far addressing this putative hypothesis in ovarian cancer patients.

Therefore, we conducted this retrospective analysis to evaluate the putative association of alopecia and chemotherapy efficacy on a sample of more than five thousand patients with primary epithelial ovarian cancer (EOC), treated with platinum- and taxane based chemotherapy regimens.

2. Patients and methods

2.1. Databases

This study was conducted using pooled single patient data from four large prospective randomised trials on platinum/paclitaxel based chemotherapy in patients with advanced primary EOC. All studies were conducted by the AGO (Arbeitsgemeinchaft Gynaekologische Onkologie)-Ovar Study Group as the leading group with cooperating groups GINECO (Groupe d'Investigateurs Nationaux pours l'Étitude des Cancers Ovariens et du sein) and NSGO (Nordic Society Gynecological Oncology). Detailed characteristics of patients and treatment protocols have been described elsewhere [11–14]. We report characteristics pertaining to our present analysis. All four trials included in all arms the cytotoxic agent paclitaxel in a three-weekly regimen, with alopecia as known side-effect (Table 1).

2.2. Patients

A total of 5114 patients, 18 years or older, with histologically proven primary EOC FIGO (Fédération Internationale de Gynécologie et d'Obstétrique)-stage [15] IIB–IV [16], who had not previously undergone any systemic treatment for ovarian cancer, were included in these four studies (AGO-Ovar 3, -5, -7 and -9) between

Table 1
Trial design of the four evaluated AGO, NSGO and GINECO studies.

AGO Ovar-study	*n*	%	Treatment regimen
3 [11]	783	15.3	Carboplatin/paclitaxel versus Cisplatin/paclitaxel
5 [12]	1282	25.1	Carboplatin/paclitaxel ± Epirubicin
7 [13]	1308	25.6	Carboplatin/paclitaxel ± Topotecan
9 [14]	1741	34.0	Carboplatin/paclitaxel ± Gemcitabine
Total	5114	100.0	