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Overview

Dose-dense Paclitaxel in Advanced Ovarian Cancer

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Abstract

Carboplatin and paclitaxel, delivered on a 3-weekly basis, is the historical standard for the management of advanced epithelial ovarian cancers (EOC). Increased dose intensity, the inclusion of additional active cytotoxic agents and lengthening treatment duration have failed to improve the outcomes seen with standard doses of carboplatin and paclitaxel in the treatment of EOC. Dose-dense (i.e. weekly) delivery of paclitaxel may exploit anticancer mechanisms such as anti-angiogenesis and the induction of apoptosis. Tumour regrowth may be more effectively impaired by the dose-dense delivery of paclitaxel. Non-randomised studies of dose-dense chemotherapy in EOC have been promising, particularly in heavily pretreated and platinum-resistant disease, with reported response rates as high as 60%. Dose-dense paclitaxel also seems to be well tolerated. These observations led to a number of comparative trials of dose-dense paclitaxel chemotherapy, three have been reported and four are ongoing. This review explores the rationale behind dose-dense delivery of paclitaxel and evaluates the results of completed phase III trials.

Key words: Advanced stage; dose-dense chemotherapy; ovarian cancer

Statement of Search Strategies Used and Sources of Information

The structure and subheadings of this article were defined by the senior author (AVT). All up to date information was accessed through three methods: PUBMED searches on key words, such as 'dose dense', 'advanced ovarian cancer', 'chemotherapy'; the American Society of Clinical Oncology meeting library for abstracts related to chemotherapy and advanced ovarian cancer; and the European Society of Gynecological Oncology meeting library for the most recent abstracts and presentations related to chemotherapy and advanced ovarian cancer.

Introduction

Progress in the management of newly diagnosed, advanced stage epithelial ovarian cancer (EOC) has reached a relative plateau in the last two decades. Maximal effort cytoreductive surgery, with the goal of debulking to the point of no visible residual disease, is the standard surgical approach. Chemotherapy with a platinum–taxane doublet, delivered intravenously postoperatively is generally accepted as the standard of care in the systemic management of advanced EOC [1–4]. Carboplatin (AUC 5–7.5) and paclitaxel (175 mg/m^2 over 3 h) delivered on a 3-weekly schedule has become the preferred regimen based on its favourable toxicity profile and ease of administration [1,2,5]. With this approach, the median time to disease progression is about 20 months and the median overall survival is close to 5 years. Intraperitoneal chemotherapy has been shown to improve median overall survival in the subset of patients with stage III, optimally debulked disease (those with <1 cm of visible residual disease at the completion of primary surgery) by up to 16 months [6–8]. However, there are some concerns about the design of past studies and the toxicity of intraperitoneal therapy [9]. Consequently, intraperitoneal therapy is not considered a standard treatment by all groups [10,11]. Triplet drug regimens have been tested, but offer no advantage over a platinum–taxane doublet [12–14]. Likewise, sequential doublets [14,15] and dose escalation to the point of stem cell support have not affected overall outcomes

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[16]. Prolonging treatment with maintenance therapy for up to 12 months in patients who respond well to first-line treatment has likewise failed to improve overall survival and is associated with added toxicity [17,18]. The use of anti-angiogenic agents has been of interest; however, to date small improvements in overall survival have only been seen on subgroup analysis [19]. These agents are expensive and may not be cost-effective, with estimates of $170 000 per life year gained [20]. Therefore, there is a need for novel highly active therapies for the treatment of EOC.

Although new active therapies for EOC remain to be identified, maximising the effectiveness of existing agents by optimising the dosing and the schedule of treatment is a sensible approach. The delivery of a given amount of drug at shorter time intervals than is standard, while maintaining the per-cycle dose and overall dose, has been referred to as dose-dense therapy [21,22]. Dose intensity refers to the dose (per unit weight or body surface area) delivered per unit time (e.g. mg/m^2/week). Therefore, dose intensity can be modified by either increasing the dose per cycle, or by reducing the time between treatments (increasing dose density). Paclitaxel is a drug whose effectiveness may be enhanced with more frequent, i.e. dose-dense, scheduling.

Rationale for Dose-dense Paclitaxel

Paclitaxel acts to stabilise microtubules, causing mitotically active cells to enter cell cycle arrest at the G2/M checkpoint [23,24]. Because it exerts its maximal cytotoxic effect on actively replicating cells, the duration and frequency of exposure to paclitaxel may be important, possibly even minimising the emergence of resistant clones [25]. Dose-dense exposure to paclitaxel may involve other mechanisms of action as well, such as induction of apoptosis or inhibition of angiogenesis [26,27]. The anti-apoptotic effects of paclitaxel were seen, independently of mitotic arrest, when cells had prolonged drug exposure (concentration and contact time) [28]. Angiogenesis inhibition is observed at non-cytotoxic doses, an effect exerted through the suppression of vascular endothelial growth factor expression [2]. Finally, early clinical data have suggested that dose-dense paclitaxel has a more favourable therapeutic index (ratio of the cytotoxic effect to the toxic effects) than standard 3-weekly paclitaxel [25].

Phase I and II Trials of Dose-dose Chemotherapy for Ovarian Cancer

Paclitaxel

Dose-dense paclitaxel has been studied in non-comparative trials. The most commonly used weekly dose is 80 mg/m^2 delivered intravenously over 1 h. In one phase I study, cumulative myelosuppression was not observed and grade 4 toxicity only reported when weekly doses reached about 100 mg/m^2/week [29]. Dose-dense paclitaxel gained interest when studies showed objective tumour responses in patients with platinum and paclitaxel-resistant EOC [30–32]. Response rates were, on average, in the 20% range, where usually less than 10% may be expected. Side-effects were minimal; typically fewer than 10% of patients experienced grade 3 or 4 toxicities. Among the grade 2 toxicities, neuropathy and fatigue were the most common (20–25 and 25–25%, respectively). Grade 2 anaemia was observed in about 35–50% of patients.

Carboplatin and Paclitaxel

The combination of carboplatin and dose-dense paclitaxel has also been extensively studied in EOC in non-randomised trials (Table 1). This combination was well tolerated and produced high response rates, even in heavily pretreated patients with platinum-resistant EOC (disease recurrence or progression within 6 months of the last line of platinum-based therapy). The compelling data from these phase II trials has led to several randomised trials in EOC.

Other Dose-dense Regimens

Other phase II trials of dose-dense regimens have been studied in EOC. Examples include dose-dense docetaxel, etoposide, docetaxel and carboplatin, topotecan and paclitaxel, and cisplatin and etoposide [37–45]. A review by van

Table 1
Phase II trials of dose-dense paclitaxel with carboplatinum in epithelial ovarian cancer

Reference	Regimen*	*n*	Platin interval	Response rate (%)	Median progression-free survival/overall survival (months)
[33]	Paclitaxel 80 mg/m^2, weekly plus carboplatin AUC = 2, weekly	27	>6 months	78	
[34]	Paclitaxel 90 mg/m^2, weekly plus carboplatin AUC4, weekly	9	≤6 months	38	
		24	>6 months	76	
[35]†	Paclitaxel 60 mg/m^2, weekly plus carboplatin AUC = 2, weekly	26	Primary treatment	38	14/32
[36]	Paclitaxel 80 mg/m^2, weekly plus carboplatin AUC = 2, weekly	64	Primary treatment	92	26/52

* Regimen details are approximate.
† This study was conducted in elderly patients (≥70 years old).