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Review

New perspectives in ovarian cancer treatment

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ABSTRACT

Ovarian cancer (OC) is increasingly understood as a heterogeneous disease comprising distinct subtypes of different origin that vary significantly with regard to molecular biology and clinical behaviour. Despite some limited progress in its treatment over the last decade, currently there are few therapeutic options and overall survival remains poor. Increasing knowledge about the molecular biology of ovarian cancer has led to the development of targeted therapies which promise to be more effective and to provide the basis for personalized treatment. The most successful strategies so far are employing anti-angiogenics (VEGF antibodies, tyrosine kinase inhibitors and angiopoietin antagonists) and polyadenosine diphosphate-ribose polymerase (PARP) inhibitors. Other approaches target aberrant OC signalling such as the PI3K/Akt/mTOR network, the epidermal growth factor receptor, the WEE1 tyrosine kinase and the folate receptor alpha. Immunotherapy is another promising new approach against ovarian cancer. In this area, immunotherapeutic modulation by administering autologous immune cells, such as dendritic cells (DCs), to stimulate antitumour host responses is of special interest. Finally, there is now growing evidence from clinical studies showing a survival advantage for intraperitoneal (IP) chemotherapy when compared to conventional intravenous treatment in the adjuvant setting. New strategies such as pressurized IP aerosol chemotherapy might further improve the efficacy of this approach.

Contents

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1. Introduction

It is estimated that each year about 220,000 new ovarian cancer (OC) cases are diagnosed and that about 140,000 women die from this disease worldwide [1]. Approximately 75% of patients present with advanced disease requiring surgery as well as platinum-based chemotherapy [2,3]. This standard treatment results in a complete response rate of 40–60%, however more than 90% of patients relapse after 18 months and with the emergence of chemoresistance ultimately die from the disease.

Increased radicality of debulking surgery and modification of dosages, numbers, schedules and combinations of conventional intravenous chemotherapies has achieved modest gains with regard to survival in OC in the last two decades. A newer approach to improve patient outcomes has been to deliver chemotherapy intraperitoneally (i.p.). Significant improvement of overall survival has been observed, however, i.p. chemotherapy is currently only suitable for optimally debulked patients in the adjuvant setting [4]. New approaches to improve efficacy of i.p. chemotherapy such as pressurized IP aerosol chemotherapy are therefore currently under investigation [5].

Recent morphologic and molecular genetic studies have shown that OC is not a single entity but a very heterogeneous disease comprising distinct subtypes of different origin that vary significantly with regard to biology and clinical behaviour [6,7]. Thus, OC is now recognized as a group of different diseases sharing the same anatomical location and requiring different therapeutic approaches which have to be tailored according the individual subtype. Increased understanding of the biology of ovarian cancer has therefore enabled the development of molecularly targeted therapies which promise to be more effective and to provide the basis for personalized treatment. The most successful strategies so far are employing anti-angiogenics and polyadenosine diphosphate-ribose polymerase (PARP) inhibitors. Other approaches target aberrant OC pathways such as the PI3K/Akt/mTOR network, the epidermal growth factor receptor, the WEE1 tyrosine kinase and the folate receptor alpha.

Immunotherapy represents another rational approach against ovarian cancer based on a body of evidence supporting a protective role of the immune system against this disease, and on the clinical success of immunotherapy in other malignancies. Immunotherapeutic modulation by administering autologous immune cells, such as dendritic cells (DCs), to stimulate antitumour host responses is of special interest in this area. Various DC based vaccines are currently part of clinical trials.

This review article aims to provide an update on the latest perspectives in the treatment of ovarian cancer.

2. Targeted therapies

2.1. Angiogenesis inhibitors

2.1.1. VEGF-antibodies/bevacizumab

Angiogenesis is an essential component of cancer growth and metastasis. It is mediated through key angiogenic molecules such as the vascular endothelial growth factor (VEGF) and its two receptors, VEGF receptor-1 (Flt-1) and VEGF receptor-2 (KDR), which are expressed on endothelial cells [8,9]. To disrupt tumour angionesis, bevacizumab (Roche, Basel, Switzerland), a humanised monoclonal antibody that inhibits the binding of VEGF to its receptors was developed [10]. In the first line treatment of ovarian cancer bevacizumab with concomitant standard 3-weekly carboplatin and paclitaxel was evaluated in two phase III trials, ICON7 and GOG218 [11,12]. In ICON-7, 1528 patients were given carboplatin (AUC 5 or 6) and paclitaxel 175 mg/m^2 every 3 weeks for six cycles with or without the addition of bevacizumab [12]. Bevacizumab was given at a dose of 7.5 mg/kg concurrently every 3 weeks for six cycles and continued for an additional 12 cycles or until disease progression. The interim analysis of the ICON7 study showed an overall progression-free survival advantage for patients receiving bevacizumab of 2.4 month in all stages (FIGO Stages I–IV). In the high-risk group (suboptimally debulked stage III with >1 cm residual disease, or stage IV) a median overall survival benefit of approximately eight months was seen with bevacizumab (HR 0.64, $p = 0.002$) [13]. Mature survival results for ICON 7 are expected in 2013.

In the GOG 218 study bevacizumab was trialled in Stage III and IV patients at a dose of 15 mg/kg every 3 weeks, for up to 15 months. During the study the primary endpoint was changed from overall survival to investigator-assessed progression-free survival and the sample size was decreased from 2000 to 1800 patients. The GOG 218 trial consisted of three treatment arms. These included (a) standard intravenous paclitaxel and carboplatin, (b) intravenous paclitaxel and carboplatin in conjunction with bevacizumab and (c) intravenous paclitaxel, carboplatin and bevacizumab with continuation of bevacizumab as a single agent for an additional 10 months as maintenance therapy. The main finding of the study was a significantly improved progression free survival of 3.8 months when bevacizumab was given concurrently with chemotherapy and continued as maintenance. However, when only RECIST and symptomatic relapse were considered, the progression-free survival (PFS) increased from 12.0 months in the placebo arm to 18.0 months in the maintenance bevacizumab arm (HR 0.645, $p < 0.001$) [12]. An overall survival benefit was not evident in GOG-218. However, as 40% in the chemotherapy-only group subsequently received bevacizumab at progression, a potential overall survival benefit would have been difficult to demonstrate.

In recurrent ovarian cancer, the phase III OCEANS study trialled bevacizumab and the combination chemotherapy carboplatin + gemcitabine in patients with recurrent platinum-sensitive disease. A significant improvement in PFS was seen with the addition of bevacizumab (8.4 vs. 12.4 months) [14]. However, the third interim overall survival analysis of this study did not show any benefit in overall survival (OS) [15]. In addition, recent data from the AURELIA study, a phase III trial in patients with recurrent platinum-resistent disease receiving bevacizumab in combination with either paclitaxel, topotecan or liposomal doxorubicin also showed a significantly improved PFS (3.4 vs. 6.7 months) [16]. The final overall survival data are expected for 2013 [17].

Based on the results from clinical studies the European Medicines Agency (EMA) approved the use of bevacizumab in combination with carboplatin and paclitaxel for the first-line treatment of patients with advanced stage ovarian cancer (FIGO IIIb, IIIc and IV) and concurrently with carboplatin + gemcitabine for second line treatment of platinum-sensitive disease [18]. However, bevacizumab has not received approval for the use neither in first line nor recurrent OC treatment by the FDA.

While neither agency considers health economics in their decision-making process, one of the greatest challenges in oncology practice today is to reconcile small clinical benefits with exponentially rising costs. Based on incremental cost-effectiveness ratio calculations from GOG218 the estimated costs per progression-free life-year saved are $479,712 in the first line setting of paclitaxel plus carboplatin plus bevacizumab and $401,088 with additional bevacizumab maintenance. The numbers are even more impressive if calculated for all patients in GOG218 (600 patients in each arm). Standard chemotherapy costs were $2.5 million, compared to $78.3 million for patients who were treated with standard chemotherapy and bevacizumab, plus additional maintenance treatments of bevacizumab for one year. Generally, if a treatment costs more than $30,000–50,000 per quality-adjusted life year, then it would not