Materials Science and Engineering C 45 (2014) 609–619

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Current treatment options and drug delivery systems as potential therapeutic agents for ovarian cancer: A review

Hongye Ye [a,*], Anis Abdul Karim [a], Xian Jun Loh [a,b,c,**]

[a] Institute of Materials Research and Engineering (IMRE), A*STAR (Agency for Science, Technology and Research), 3 Research Link, Singapore 117602, Singapore
[b] Department of Materials Science and Engineering, National University of Singapore, 9 Engineering Drive 1, Singapore 117576, Singapore
[c] Singapore Eye Research Institute, 11 Third Hospital Avenue, Singapore 168751, Singapore

ARTICLE INFO

Article history:
Received 2 April 2014
Accepted 9 June 2014
Available online 20 June 2014

Keywords:
Ovarian cancer
Intraperitoneal
Chemotherapy
Drug delivery
Nanoparticles
Co-delivery

ABSTRACT

Ovarian cancer is one of the most common and deadliest gynecologic cancer with about 75% of the patients presenting in advanced stages. The introduction of intraperitoneal chemotherapy in 2006 had led to a 16 month improvement in the overall survival. However, catheter-related complication and the complexity of the procedure had deterred intraperitoneal route as the preferred route of treatment. Other alternative treatments had been developed by incorporating other FDA-approved agents or procedures such as pegylated liposomal doxorubicin (PLD), hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) and the administration of bevacizumab. Various clinical trials were conducted on these alternatives as both the first-line treatment and second- or third-line therapy for the recurrent disease. The outcome of these studies were summarized and discussed. A prospective improvement in the treatment of ovarian cancer could be done through the use of a drug delivery system. Selected promising recent developments in ovarian cancer drug delivery systems using different delivery vehicles, surface modifications, materials and drugs were also reviewed.
© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Ovarian cancer is the fifth leading cause of cancer-related deaths among women. It is one of the most common and the deadliest gynecologic cancer, with reported 14,436 deaths in 2009 and a projected incidence of about 21,980 and deaths of about 14,270 in 2014 [1,2]. About three-quarters of patients who present with peritoneal metastasis at the time of diagnosis [3,4] had a five-year survival rate of merely 26.9% [1,2]. Ovarian cancer is relatively asymptomatic at its early stages with rare cases of incidental early diagnosis due to other diseases or symptoms, and this led to low chance of early detection [3].

The Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) developed an ovarian cancer staging system, the most common staging criteria used. A brief summary of each stage has been included in Table 1 [5]. Tumor cells could metastasize to within the vast capacity of the pelvis and the ovaries before stage III. By the time patients present with symptoms such as loss of weight, abdominal bloatedness and early satiety, metastasis had occurred into and beyond the peritoneal cavity. Although patients with low-risk, stage I cancer could expect to have a five-year-survival rate of greater than 90%, approximately 75% of ovarian cancer patients present only in stages III and IV, having survival rates of 30%–50% and 13% respectively [6–9].

2. Current treatment options

Early stage ovarian cancer patients would undergo either prophylactic oophorectomy or salpingo oophorectomy, shown to greatly improve chance of survival. No chemotherapy is required post-surgery unless the tumors are of grade III and above. Patients with early stage ovarian cancer are currently undergoing clinical trials for chemotherapy and radiation therapy after surgery for additional benefits on survival [5,10–14]. The first-line standard treatment for advanced stage ovarian cancer patients includes an optimal cytoreduction surgery — tumors greater than a diameter of 1 cm are removed (most often via a minimally invasive laparoscopic surgery), followed by intravenous (IV) or intraperitoneal (IP) chemotherapy with a platinum-based agent such as cisplatin (Fig. 1A) and taxol such as paclitaxel (Fig. 1C) [8,15,16]. The IV therapy involves six cycles of IV platinum (75 mg/m^2 of cisplatin or AUC 6 or 7 of carboplatin (Fig. 1B), calculated using the Calvert formula) and paclitaxel (135 mg/m^2) once every three weeks [17,18]. Patients recommended for IP chemotherapy receive 135 mg/m^2 of paclitaxel IV after the optimal cytoreductive surgery, followed by 100 mg/m^2 of cisplatin and 60 mg/m^2 of paclitaxel through an implanted catheter once every three weeks, for six cycles [18]. The catheter and its attached subcutaneous port for regular IP drug solution infusion are implanted during the cytoreduction surgery.

* Corresponding author. Tel.: +65 6514 8746.
** Correspondence to: X.J. Loh, Department of Materials Science and Engineering, National University of Singapore, 9 Engineering Drive 1, Singapore 117576, Singapore. Tel.: +65 6513 1612.
E-mail addresses: yehy@imre.a-star.edu.sg (H. Ye), lohxj@imre.a-star.edu.sg (X.J. Loh).

http://dx.doi.org/10.1016/j.msec.2014.06.002
0928-4931/© 2014 Elsevier B.V. All rights reserved.

Table 1
A description of the FIGO staging system for the diagnosis of ovarian cancer [5].

	Stages	Description
Early stages	I	Tumor growth is confined to the ovaries.
	II	Tumor growth is confined to the pelvic region.
Late stages	III	Metastasis to the organs of the peritoneal cavity (omentum, small intestines, superficial surface of the liver etc) and/or regional lymph nodes.
	IV	Distant metastasis beyond the peritoneal cavity.

The Gynecology Oncology Group (GOG) had conducted three large randomized phase III trials, comparing IV cisplatin treatment regimens to IP cisplatin treatment [17–20]. The group concluded that IP cisplatin treatment regimen was able to prolong overall survival from 49.7 months in IV treatment to 65.6 months ($p = 0.03$) [18]. This vast improvement in overall survival of 16 months was rarely observed in clinical trials. However, while 83% of subjects completed all cycles of the IV therapy, only 42% of subjects completed all cycles of the IP therapy. The primary reason for early termination of the IP treatment was catheter-related complications [21,22]. The implantation site was susceptible to infection and inflammation over the entire 18 weeks period of treatment, and the long catheter was susceptible to obstruction [22]. Furthermore, many medical practitioners in smaller centers were unable to recommend the treatment modality due to lack of familiarity among clinicians with this intraperitoneal administration and catheter-placement techniques [18,23]. Additional criticism on IP chemotherapy was that although local drug concentration was higher than systemic drug concentration, the drug penetration depth into the tumor tissue was only around 1–3 mm [24–26]. IP chemotherapy would therefore only be recommended for patients with small residual tumors in the peritoneal cavity after the cytoreduction surgery [21,27]. This implied more extensive tumor debulking and therefore set more demanding criteria for surgery.

For the reasons illustrated above, IP chemotherapy proved to benefit only a small portion of patients with advanced ovarian cancer. The most widely practiced first-line treatment regimen remained as six cycles of IV platinum (preferably carboplatin) with paclitaxel infusion once every three weeks. Carboplatin (Fig. 1B), an analog to cisplatin that was later developed with more tolerable side-effects in patients, had only been approved for IV administration. An ongoing clinical trial was conducted by the GOG (GOG 252), comparing treatment outcome of IV versus IP carboplatin with the maintenance of bevacizumab to verify carboplatin treatment in IP administration [28]. In general, poor treatment outcome and high relapse occurrence in ovarian cancer indicated further efforts to improve the therapeutic regimen for ovarian cancer patients.

3. Adjuvant therapies

3.1. Increased number of courses of treatment

Two independent groups of researchers conducted clinical trials to investigate the effect of increased number of treatment courses on the outcome of treatment. One group compared five cycles versus ten cycles of treatment with cyclophosphamide, doxorubicin (Fig. 1D) and cisplatin at a frequency of one cycle for every four weeks. The results showed that ten cycles of treatment induced higher toxicity myelosuppression, hospital admission for nadir fever, nephrotoxicity and neurotoxicity than the five cycles of treatment while causing no improvement to the number of complete responses and survival [29]. A phase III clinical trial was also conducted to observe the effect of no further treatment versus six further courses of paclitaxel after the usual six courses of platinum and paclitaxel IV chemotherapy. The trial showed that the extra six courses of paclitaxel failed to prolong either OS or PFS [30].

3.2. Third therapeutic agent

Attempts to improve the treatment outcome of ovarian cancer in recent years included the addition of a third cytotoxic agent to the current IV regimen [31]. A multinational collaborative phase III clinical trial was conducted by the Gynecologic Cancer InterGroup (GCIG) to investigate the change to the overall survival (OS) and progression-free survival (PFS) of advanced-stage ovarian cancer patients after either topotecan, gemcitabine or methoxypolyethylene glycosylated liposomal doxorubicin (PLD) was incorporated to the standard IV carboplatin and paclitaxel treatment regimen. Results from 4312 patient enrolled showed that the addition of the three agents did not cause any statistically significant improvements to OS or PFS. PLD will be described in detail in Section 3.3.

3.3. Liposomal formulation

Doxorubicin belongs to a class of drug called anthracycline (Fig. 1D), a cytostatic antibiotic used to treat various types of cancers such as breast cancer, lymphoma, leukemia and ovarian cancer [32]. Anthracycline was used as the first-line treatment for ovarian cancer before the introduction of taxanes. Doxorubicin is a topoisomerase II inhibitor and promotes tumor cell DNA fragmentation. Its antitumor activity and drug toxicity can also be resulted from the formation of oxygen free radicals when doxorubicin is reduced inside the cell [33]. However, it is also associated with severe cardiotoxicities such as cardiomyopathy and congestive heart failure [32,34,35].

The pegylated liposomal doxorubicin or methoxypolyethylene glycosylated liposomal doxorubicin (PLD) as shown in Fig. 2 aimed to reduce the side effects of free doxorubicin and to enhance its antitumor activities. The liposomes, approximately 100 nm in diameter, prevent the drug from entering healthy tissues such as cardiac and gastrointestinal tissues, thus reducing its toxicity to those organs [35,37,38]. The poly (ethylene glycol) layer around the liposome is hydrophilic, preventing the attack of reticuloendothelial system in the systemic circulation. PLD has more favorable pharmacokinetics compared to free doxorubicin. The volumes of distribution of PLD and free doxorubicin *in vivo* were 4.1 L and 254 L respectively, and the plasma clearance rate was 0.08 L/h and 45.3 L/h respectively [33]. Consequently, the elimination half-life of PLD was found to be 20–30 h therefore PLD has a larger area under the concentration time curve (AUC) that is at least 60-fold that of free doxorubicin [39].

The promising pharmacokinetics of PLD called forth multiple phase I, II and III trials to investigate the treatment outcome of PLD in ovarian cancer patients at different stages of the disease progression. A randomized, multicenter phase III clinical trial was conducted to compare carboplatin/PLD regimen with the standard carboplatin/paclitaxel regimen in platinum-sensitive relapse or recurrent ovarian cancer patients after first- or second-line platinum/taxane-based therapies [40]. This trial involving 976 patients proved that carboplatin/PLD arm had a statistically significantly longer PFS of 11.3 months versus 9.4 months in the carboplatin/paclitaxel arm ($p = 0.005$, hazard ratio $= 0.821$). There was a higher incidence of alopecia, sensory neuropathy and hypersensitive reaction in the carboplatin/paclitaxel arm, while the carboplatin/PLD arm experienced more hand–foot syndrome, nausea and mucotitis [40,41]. The superiority of PLD in prolonging PFS and its reduced neurotoxicity suggested the possibility of including PLD as a first-line treatment agent.

Two main phase III trials were conducted to compare the treatment outcome of carboplatin/paclitaxel versus carboplatin/PLD as a first-line treatment for ovarian cancer. The Multicenter Italian Trials in Ovarian Cancer-2 (MITO-2) enrolled 820 patients with stage III to IV ovarian cancer [41]. Carboplatin was dosed at an AUC of 5 (Calvert formula) and paclitaxel was dosed at 175 mg/m^2 once every three weeks in the standard arm. The experimental arm dosed patients at AUC 5 of carboplatin and 30 mg/m^2 of PLD once every three weeks.

Download English Version:

https://daneshyari.com/en/article/1428515

Download Persian Version:

https://daneshyari.com/article/1428515

Daneshyari.com