Biomaterials 34 (2013) 1073–1101

Contents lists available at SciVerse ScienceDirect

Biomaterials

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

Review

Nanocarriers for the targeted treatment of ovarian cancers

Julie Tomasina [a,b], Stéphanie Lheureux [b,c], Pascal Gauduchon [b], Sylvain Rault [a], Aurélie Malzert-Fréon [a,*]

[a] Université de Caen Basse-Normandie, EA 4258 CERMN, FR CNRS 3038 INC3M, SF 4206 ICORE, UFR des Sciences Pharmaceutiques, F-14032 Caen, France
[b] Université de Caen Basse-Normandie, EA 4656 BioTICLA, Centre de Lutte Contre le Cancer F Baclesse, SF 4206 ICORE, UFR des Sciences Pharmaceutiques, F-14032 Caen, France
[c] Département d'oncologie médicale, Centre de Lutte Contrele Cancer F Baclesse, F-14032 Caen, France

ARTICLE INFO

Article history:
Received 18 July 2012
Accepted 23 October 2012
Available online 20 November 2012

Keywords:
Ovarian cancer
Drug delivery systems
Active targeting
Strategies

ABSTRACT

Ovarian cancer is the leading cause of death from gynecological malignancies worldwide. Although the majority of tumors initially respond to standard treatments combining surgery and chemotherapy with platinum based chemotherapy, frequent recurrence and subsequent acquired chemoresistance are responsible for the therapeutic failure, leading to an overall 5 years survival rate of 30%. Considering the usual initial sensitivity of the ovarian tumors to chemotherapy, over the past decade efforts have been focused over the past decade to cure ovarian cancer using the currently available chemotherapeutic agents in various combinations, dosages, schedules (durations and/or routes of administration). However, with such a systemic chemotherapeutic approach, considerable limitations exist including toxicities to healthy tissues and low achievable drug concentrations at tumor sites. Considerable efforts are implemented to engineer systems capable of ferrying large doses of cytotoxic agents specifically into targeted malignant cells while sparing healthy cells. The purpose of the present review is to index the main targeted colloidal systems used for drug delivery to ovarian tumors. These nanocarriers will be analyzed by citing examples of their use in preclinical development.

1. Introduction

1.1. Epidemiologic data on ovarian cancers

Ovarian cancers are the leading cause of deaths from gynecological malignancies worldwide and the fifth most common cause of cancer death in women [1]. In 2008, more than 224,000 new diagnoses, and 140,000 deaths occurred from this neoplasm in the world [2] with less than 40% of women who can be cured of the disease. The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life, with a rate of 57 per 100,000 women. The median age at diagnosis is 63 years.

Epithelial ovarian cancers represent 90% of ovarian cancers. They could derive from ovarian surface epithelium cells, or from fallopian tubal epithelium cells [3,4]. In comparison with other solid tumor types, ovarian carcinomas present peculiar and varied development and dissemination processes. Two main development types are observed. If tumors grow slowly, and remain confined to the ovary, ovarian carcinomas are said type I. They include serous, mucinous, endometrioid and clear cell carcinomas. If tumors are more aggressive, they are said type II; they include high grade serous carcinomas, malignant mixed mesodermal tumors, and undifferentiated carcinomas [5].

About 70% of patients are diagnosized with advanced disease (FIGO III/IV tumor stages). At these stages, numerous tumor nodes are present and disseminated throughout the peritoneal cavity. Presence of tumoral nodes clearly impact on the behavior of the tumor and on the success of the treatment [6]. Furthermore, ascites can constitute a reservoir of aggressive cancer cells, and presence of ascitic fluids can also facilitate peritoneal dissemination by carrying cancer cells in the peritoneal cavity.

Therefore, any treatment should be able to target various kinds of tumoral cells and/or tissues.

1.2. Standard therapeutic management of ovarian cancers

The standard initial management of advanced stages is a cytoreductive surgery [7]. It has to be as complete as possible since it is the most powerful determinants of cohort survival [8].

At the present, this treatment is followed by a current standard chemotherapy based on the association of carboplatin-paclitaxel given intravenously every 21 days for six cycles [9]. An interesting alternative is the carboplatin/weekly paclitaxel schedule [10]. A phase III has shown that dense dose of carboplatin/paclitaxel improves long-term progression free survival and overall survival in patients with advanced epithelial ovarian cancer [11].

* Corresponding author. Tel.: +33 231 566819; fax: +33 231 566020.
E-mail address: aurelie.malzert-freon@unicaen.fr (A. Malzert-Fréon).

0142-9612/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.biomaterials.2012.10.055

Intravenous docetaxel plus carboplatin [12] or paclitaxel plus cisplatin [13] are options in case of paclitaxel reaction.

So far, despite an initial 70–80% response rate, most patients relapse due to the development of disease resistant to chemotherapy. The delay before disease relapse is taken into consideration to determine chemotherapy retreatment (Table 1).

The carboplatin/paclitaxel combination is regarded as a valid option for rechallenge in patients with platinum-sensitive recurrent ovarian cancer. However, this approach has been limited by the risk of cumulative peripheral neuropathy.

More generally speaking, considering the initial sensitivity of the ovarian tumors to the chemotherapy, efforts have been made over the past decade to cure ovarian cancer using the currently available chemotherapeutic agents in various combinations, dosages, durations of administration, and/or routes of administration [14–16]. In particular, results of clinical trials have shown a better effectiveness of the cisplatin when the amounts used are doubled [17,18]. However, associated toxicity of high-dose chemotherapy is an obstacle to this approach. Indeed, anticancer agents are low-molecular-weight drugs presenting a low bioavailability, and a non-specific body distribution, *i.e.* they do not act exclusively on cancer cells. Thus, use of high dose of these molecules results in severe systemic toxicity and poor patient compliance [19].

These results point the need for significant improvements by different ways like use of interesting pharmacological chemotherapy agents, other therapeutic strategy administration and new targeted agents.

1.3. Alternatives to standard chemotherapy on ovarian cancers

1.3.1. Use of the intraperitoneal route as chemotherapeutic administration way

Intraperitoneal use of cisplatin after optimum surgical cytoreduction could be an attractive alternative to improve chemotherapy in patients with epithelial ovarian cancer [20,21]. However, intraperitoneal chemotherapy has not been universally accepted for at least three reasons: toxic effects, intraperitoneal treatment delivery issues (e.g., technical experience with catheter placement and management), and complications (e.g., intraperitoneal adhesions, infections) [22].

1.3.2. Development of targeted drugs

New drugs were developed, and among them, monoclonal antibodies have been designed to specifically target tumor cells, tumor stroma, tumor vasculature, and cellular signaling mechanisms that are aberrant in tumor tissues. With such targeted drugs, tumoral tissue is more precisely targeted than with traditional cytotoxic anticancer drugs. Moreover, whereas growth retardation and apoptosis are induced, the toxicity to normal cells is reduced.

1.3.2.1. Inhibition of the VEGF pathway. Among targeted drugs developed for the treatment of ovarian cancer, some of them were designed to inhibit angiogenesis, the growth of new blood vessels.

Table 1
Ovarian cancer classification.

Terminology	Definition
Platinum refractory ovarian cancer	Disease progression during the initial platinum based chemotherapy
Platinum resistant ovarian cancer	Disease relapse or progression within 6 months after the first line chemotherapy
Partial platinum sensitive ovarian cancer	Disease relapse within a period of between 6 and 12 months after the end of initial chemotherapy
Platinum sensitive ovarian cancer	Disease relapse after a period of 12 months after completion of initial platinum based therapy

The vascular endothelial growth factor (VEGF) pathway has been shown to play a pivotal role in the progression of ovarian cancer leading to the development of malignant ascites. Even if VEGF pathway is considered to be the key driver of angiogenesis, the platelet-derived growth factor (PDGF) and the fibroblast growth factor (FGF) pathways also play important roles, and may contribute to resistance to VEGF-specific blockade [23].

On this basis, agents rendering VEGF ineffective by neutralizing VEGF, blocking its receptors, or interfering with the postreceptor signaling pathways have been developed [24]. As shown in Table 2, different antiangiogenesis drugs are currently evaluated.

Results of clinical trials about therapies targeting tumor-supportive angiogenesis and associated growth factors are showing promising. Nevertheless, some unintended toxic effects have emerged from phase I and II trials of agents with anti-angiogenic properties in ovarian cancers. Hypertension is one of the most common side-effects of antiangiogenic therapy. Proteinuria, cardiac toxicity, vascular thromboembolism, hemorrhage, gastrointestinal toxicity, dermatological toxicity like hand-foot skin reaction or acral erythema, endocrine toxicities like thyroid dysfunction or hypoglycemia are also reported. From that, some authors recommend vigilance by oncologists to appropriately manage such collateral damages stemming from targeted and antiangiogenic agents [25,26].

Moreover, some preclinical data show that in certain malignancies antiangiogenic treatment while efficiently driving to a decrease in tumor size will also induce higher malignancy stages and increase distant metastasis. Given the short feedback of clinical use of these agents, this possible issue should be carefully monitored [27].

However, bevacizumab (Avastin®) is already approved in first line chemotherapy, in addition with standard chemotherapy, *i.e.* with iv association of carboplatin-paclitaxel every 21 days for 6 cycles, on patients at high risk of progression [28–30].

1.3.2.2. Inhibition of other pathways. Drugs targeting other pathways are also studied (Table 3).

Table 2
Antiangiogenesis agents in clinical development for ovarian cancer.

	Drugs	Molecular target	Phase of development
VEGF ligand binders	VEGF: bevacizumab	VEGFA (all isoform)	Approved
	VEGR trap: aflibercept	VEGFA and B, PlGF	Phase II
VEGF receptor tyrosine kinase inhibitors	Ramucirumab	VEGFR2	Phase II
	Cediranib	VEGFR1-3, c-kit, PDGFR-β	Phase II
	Semaxinib	VEGFR2	
Multiple receptor tyrosine kinase inhibitors	Sunitinib	VEGFR1-3, Flt-3, PDGFRα, PDGFR-β, c-kit, CSF-1R, RET	Phase II
	Sorafenib		Phase II
	Vatalanib		Phase II
	Intedanib (BIBF 1120)	VEGFR1-3, Flt-3, PDGFR-β, c-kit, Raf-1	Phase III
			Phase III
	Pazopanib	VEGFR1, PDGFR-β, c-kit, Fms	Phase II
	Motesanib	VEGFR1-3, PDGFRα, PDGFR-β, FGFR1-3	
	Vandetanib	VEGFR1-2, PDGFR-β, c-kit	
		VEGFR1-3, PDGFR, c-kit	
		VEGFR2-3, EGFR	
Angiopoietin receptor (Tie2 receptor) peptide–Fc fusion protein	AMG 386	Angiopoietin 1-2	Phase III