Metronomic Chemotherapy in Gynecological Cancers

14

Victoria A. Forte and Agustin A. Garcia

Abstract

Ovarian cancer is the 5th leading cause of cancer mortality in the United States, and despite major advances in cytoreductive surgery and the use of chemotherapy with a platinum and a taxane in the first-line setting, recurrence is still a common problem. Efforts to improve the efficacy of conventional chemotherapy have been resulted in general in limited benefit. Metronomic chemotherapy represents an alternate schedule of chemotherapy administration. Preclinical and clinical data attest to the efficacy of metronomic chemotherapy as a treatment modality in ovarian cancer. Further research, including phase III clinical studies, is required to determine the role of this promising therapeutic approach in the management of ovarian cancer.

14.1 Introduction

Ovarian, endometrial, and cervical cancers represent the most common gynecological tumors. Of these, ovarian cancer is the most lethal. It is estimated that in 2013 in the United States 22,240 women will be diagnosed with and 14,030 women will die of ovarian cancer, making ovarian cancer the fifth leading cause of cancer death [1]. While advances in cytoreductive surgery and the use of first-line chemotherapy with platinum and taxane have increased disease-free survival and overall survival [OS], recurrence is still a common problem [2]. Most patients present with advanced disease [stage III–IV], and only 25–30 % of them are alive at 5 years [1, 2]. Treatment for recurrent platinum-sensitive disease can achieve long-term control [3, 4]. However, all patients with recurrent disease will eventually develop resistance to platinum. In this setting, several agents, such as pegylated liposomal doxorubicin, topotecan, taxanes, etoposide, and gemcitabine, have activity [2]. However, response rates to single agent are only 10–25 %, and median survival is less than 1.5 years [5].

V.A. Forte, MD • A.A. Garcia, MD (✉)
Division of Medical Oncology, University of Southern California, Los Angeles, CA, USA
e-mail: aagarcia@usc.edu

G. Bocci, G. Francia (eds.), *Metronomic Chemotherapy: Pharmacology and Clinical Applications*, DOI 10.1007/978-3-662-43604-2_14,

Combination chemotherapy is frequently associated with a higher response rate and increased toxicity, but this has not translated into improved survival [6–8].

Metronomic chemotherapy represents an alternative to using more intense, toxic chemotherapy regimens in patients with recurrent ovarian cancer. The mechanisms of action and preclinical studies of metronomic chemotherapy are presented in detail in Chaps. 2 and 3 of this book. Briefly, standard chemotherapeutic regimens are designed to deliver the highest or maximum tolerated dose [MTD], which can be safely administered [9]. Due to detrimental effects on normal tissues, rest periods of typically 3–4 weeks are required between treatments and to minimize toxicity. However, recent studies indicate that tumor-associated endothelial cells continue to proliferate and promote cancer growth between treatments [10, 11].

Therefore, the "more is better" philosophy may not be ideal. To avoid the toxicities and morbidity caused by conventional chemotherapeutic regimens and improve the quality of life of cancer patients, several groups had studied a new modality of drug administration: metronomic chemotherapy [12]. This term was first used by Douglas Hanahan, who also emphasized the concept of "less is more" and demonstrated the antiangiogenic effect of metronomic dosing of cytotoxic agents in mice [13].

Similar definitions include the administration of cytotoxic drugs on a more continuous basis, with a much shorter break period, or none at all, and generally at lower doses of various cytotoxic drugs or combinations with other newer, targeted therapies, like antiangiogenesis agents [14].

Metronomic chemotherapy is associated with lower treatment-related toxicity than conventional maximum tolerated dose (MTD) chemotherapy, and phase II/III trials are revealing that it is active [15].

It has been proposed that metronomic chemotherapy exerts its antitumoral effects primarily by inhibiting angiogenesis and regulating immune response [11, 16]. In preclinical models, virtually every class of chemotherapeutic agent administered on a metronomic schedule has been shown to inhibit angiogenesis, which contributes to their antitumor efficacy [17]. Furthermore, impressive antiangiogenic and antitumor effects and reduced toxicity have been observed in mice [18]. In the rest of this chapter, we will discuss the experimental and clinical data that has investigated the efficacy and toxicity of metronomic chemotherapy in gynecological tumors. As virtually all research has been conducted in ovarian cancer, we will limit our discussion to this disease.

14.2 Metronomic Chemotherapy in Ovarian Cancer

The management of ovarian cancer begins with appropriate surgical staging and tumor debulking followed by platinum-based chemotherapy. The administration of 6 cycles of intravenous carboplatin and paclitaxel represents the standard treatment for patients with stage III–IV [2]. However, in early disease the optimal number of cycles has not been determined [19]. Over the last 20 years, several strategies have

been evaluated to improve the outcome of ovarian cancer. Some, such as the addition of a third cytotoxic chemotherapy agent, have been completely unsuccessful [20]. Others have clearly shown an improved outcome in randomized trials. For example, the administration of intraperitoneal chemotherapy [IP] has consistently shown an improvement in survival in patients with optimally debulked ovarian cancer [21–23]. However, for various reasons, this approach is not widely used [24]. Recent studies suggest that the use of paclitaxel on a dose-dense schedule improves survival [25]. This approach awaits confirmation from other studies. The addition of bevacizumab was shown to have modest effects [26, 27].

Another approach that was studied to improve the outcome of ovarian cancer was to administer paclitaxel as a maintenance treatment after completing standard chemotherapy with carboplatin and paclitaxel. In protocol SWOG 9761/GOG 178, patients with stage III ovarian cancer who had no evidence of disease after completing 6 cycles of standard treatment were randomized to receive 3 or 12 additional cycles of paclitaxel at a dose of 175 mg/m^2 [28]. In GOG 175, patients with stage I–II disease were randomized to maintenance treatment with 24 weeks of low-dose paclitaxel or observation after 3 cycles of intravenous carboplatin and paclitaxel [29]. The results of these trials are discussed later in this chapter and are summarized in Table 14.1.

Patients with recurrent ovarian cancer are categorized into two major groups. Patients who relapse more than 6 months after completing platinum-based chemotherapy are classified as "platinum sensitive," and standard treatment includes retreatment with a platinum-based regimen. Combination regimens appear to be superior to single-agent platinum [3, 4].

Patients who relapse or progress within 6 months of their last platinum-based regimen are considered platinum resistant. All patients with recurrent ovarian cancer will eventually become platinum resistant and are then treated with non-platinum agents such as pegylated liposomal doxorubicin, topotecan, taxane (docetaxel or weekly paclitaxel), gemcitabine, and others. These patients are typically treated with sequential single agents. Although there is limited data, combination cytotoxic chemotherapy is frequently associated with an improved response rate but no improvement in overall survival at the cost of increased toxicity [6–8, 30, 31].

In the next sections, we discuss the experimental and clinical data evaluating the role of metronomic chemotherapy in ovarian cancer, both when used as frontline therapy and in recurrent disease.

14.3 Paclitaxel

The introduction of paclitaxel to frontline treatment leads to a significant improvement of survival in ovarian cancer. Paclitaxel is frequently administered at a maximal tolerated dose every 3 weeks in the initial treatment of ovarian cancer. In vitro data suggest that the duration of exposure plays a crucial role in the cytotoxicity of paclitaxel [32, 33]. Weekly administration of paclitaxel has the potential to have an effect similar to that of continuous infusion while taking advantage of the

Table 14.1 Phase III randomized trials evaluating modifications to carboplatin and paclitaxel as treatment of ovarian cancer

Study	Treatment	Results		Grade 3/4 toxicities (%)		
		PFS	OS			
GOG178/SWOG9761	Paclitaxel 175 mg/m IV q 4 weeks	Median PFS	NR		3 cycles	12 cycles
Stage III	3 cycles	21 m				
Maintenance treatment	12 cycles	28 m		Neutropenia	10	4
$N=277$ (Markman)		HR = 2.31		Neuropathy (grade 2/3)	15	23
		$P=0.023$				
GOG 157	Carboplatin/paclitaxel	5 years PFS	5 years OS		3 cycles	6 cycles
3 vs. 6 cycles	IV q 3 weeks	75 %	81 %	Neutropenia	78	85
		80 %	83 %	Anemia	4.7	6.6
Stage I/II	3 cycles	HR = 0.761	HR = 1.02	Gastrointestinal	4.7	8.9
$N=457$ (Bell)	6 cycles	$P=0.18$	$P=0.94$	Neuropathy	1.8	11.3
GOG 172	IV vs. IP Carboplatin/paclitaxel	Median PFS	Median OS	Leukopenia	IV	IP
				Thrombocytopenia	64	76
IP chemotherapy	IV	18.3 m	49.7 m	Gastrointestinal	4	12
		23.8 m	65.6 m	Renal	24	46
Stage III optimally debulked	IP	HR = 0.77	HR = 0.73	Neuropathy	2	7
				Infection	9	19
$N=429$ (Armstrong)		$P=0.05$	$P=0.03$	Fatigue	6	16
				Metabolic	4	18
				Pain	7	27
					1	11
GOG 218	Carboplatin/paclitaxel IV q 3 weeks × 6	Median PFS	Median OS		Placebo	Bevacizumab
Stage III	Placebo	10.3 m	39.3 m	Thrombocytopenia	15	21
		14.1 m	39.7 m	Hypertension	1.6	10
$N=1,248$ (77)	Bevacizumab 15 mg/kg IV q 3 weeks × 20 cycles	HR = 0.71	HR = 1.03	Constitutional	10	13
		$P=0.001$	$P=0.45$	Gastrointestinal	7.9	19

JGOG 3016	Carboplatin/paclitaxel IV × 6 cycles	Median PFS	Median OS	Neutropenia	Standard	Dose dense
Stage III	Paclitaxel 175 mg/m^2 q 3 weeks	17.5 m	62.2 m	Thrombocytopenia	88	92
		28.2 m	100.5	Anemia	38	44
Dose-dense paclitaxel	Paclitaxel 80 mg/m^2 q 1 week	HR = 0.76	HR = 0.79	Neuropathy	44	69
N = 631 (Katsumata × 2)		*P* = 0.0037	*P* = 0.039		10	12
GOG 175	Carboplatin/paclitaxel IV q 3 weeks × 3	5 years PFS	5 years OS	Neutropenia	Observation	Weekly paclitaxel
Low-dose paclitaxel	Observation	77 %	85.4 %	Cardiovascular	74	75
		80 %	86.2 %	Gastrointestinal	2.6	4.4
Stage I/II	Paclitaxel 40 mg/m^2 weekly × 24	HR = 0.80	HR = 0.78	Infection	4.1	4.5
N = 571 (mannel)		*P* = 0.24	*P* = 0.23	Neuropathy	4.1	5.5
					0.7	4.4

minimal hematological toxicity associated with shorter infusions [34]. Several clinical trials, in ovarian cancer as well as other tumors, have reported that patients who became resistant to this schedule were found to have a high response to paclitaxel administered at a lower dose every week [34–38]. In addition, toxicity, particularly myelosuppression, was decreased.

In summary, clinical trials demonstrated that weekly paclitaxel administered at a dose of 80 mg/m^2 is one of the most active regimens in recurrent platinum-resistant ovarian cancer [35, 36]. In addition, as mentioned above, the substitution of conventional paclitaxel for weekly [or dose-dense] paclitaxel, in combination with carboplatin, was reported to significantly improve progression-free and overall survival in a phase III randomized trial in patients with stage III–IV disease.

The use of an even lower dose of weekly paclitaxel was evaluated in protocol GOG 175 [29]. In this study, patients with stage I or II ovarian cancer were treated with 3 cycles of conventional carboplatin and paclitaxel and were then randomized to observation or 24 weeks of low-dose (40 mg/m^2) paclitaxel. Although it did not achieve statistical significance, the recurrence rate was 19.3 % lower for those randomized to weekly paclitaxel, hazard ratio (HR) 0.807 (95 % CI, 0.565–1.15, $P=0.24$). Similarly, the death rate was 21.9 % lower in the paclitaxel arm (HR 0.781; 95 % CI, 0.522–1.17; $P=0.23$).

The addition of weekly paclitaxel modestly increased toxicity as the incidence of grade 2 or worse peripheral neuropathy (15.5 % vs. 6.0 %), infection or fever (19.9 % vs. 8.7 %), and dermatologic events (70.8 % vs. 52.1 %) was higher ($P<0.001$). There was also a slightly greater incidence of grade 2 or worse cardiovascular events (8.1 % vs. 3.8 %, $P=0.044$) among those on the maintenance regimen. Grade 3 or 4 peripheral neuropathy was reported in 0.7 % of the observation group compared to 4.4 % of the maintenance paclitaxel group ($P=0.012$).

Within the limitation of cross comparison among clinical trials, the results of using low-dose weekly paclitaxel as part of the frontline treatment of ovarian cancer compare favorably with other strategies developed to improve the outcome of ovarian cancer such as IP chemotherapy, maintenance paclitaxel administered at full doses, or additional cycles of carboplatin and paclitaxel (3 vs. 6). Table 14.1 summarizes the HR of these strategies and their toxicities.

It is interesting to observe the clinical application and interpretation of these studies by the medical community. In three large randomized clinical trials and in a meta-analysis [39], IP chemotherapy has been shown to significantly improve overall survival. This led to a clinical alert by the National Cancer Institute (NCI) recommending that IP chemotherapy should be considered in patients with small-volume disease [40]. Treatment guidelines in the United States (National Comprehensive Cancer Network-NCCN and NCI) recommend it use [30]. However, IP chemotherapy is not widely used. On the other hand, evaluating the same data, treatment guidelines by the European Society of Medical Oncology (ESMO) do not fully endorse their use [41]. Similarly, the use of dose-dense weekly paclitaxel is recommended by the NCCN, while ESMO does not consider it a standard of care.

The interpretation of the other studies listed in Table 14.1 is also interesting. Strictly talking, none of the remaining studies (GOG 178, GOG 157, GOG 218, and

GOG 175) met their primary end point as they failed to demonstrate a statistically significant improvement in overall survival. GOG 178 and GOG 218 did demonstrate a statistically significant improvement in PFS that did not translate to an improvement in OS. Despite this, both approaches are included as recommended treatments in the NCCN guidelines, although with level of recommendation grade 2B and 3, respectively. On the other hand, ESMO guidelines do not even address the role of maintenance chemotherapy while they endorse the addition of bevacizumab. GOG 157 did not demonstrate a benefit for administering 6 cycles of chemotherapy to patients with early disease. Nonetheless, NCCN recommends the use of 3–6 cycles of carboplatin and paclitaxel, while ESMO recommends single-agent carboplatin [55, 68].

Of interest, no organization recommends or discusses the use of low-dose weekly paclitaxel, a true metronomic schedule, as used in GOG 175. Granted, this trial failed to demonstrate a statistically significant improvement in PFS or OS. However, the magnitude of the observed benefit (HR of 0.80 and 0.78) and the toxicity profile compare favorably with the findings reported in GOG 178, 157, and 218 which are endorsed by guidelines and/or are commonly used in the community.

14.4 Cyclophosphamide

The antiangiogenic effect of cyclophosphamide was first demonstrated in a murine model of cyclophosphamide-resistant tumors designed to rescue mice by inducing endothelial apoptosis [42]. Clinical activity was reported in solid tumors, such as breast cancer [43].

The potential role for metronomic cyclophosphamide in ovarian cancer was first described by Samaritani who reported the case of a 36-year-old woman with stage IIIC ovarian cancer who failed chemotherapy with paclitaxel and carboplatin as first line and progressed after second line with topotecan. She was placed on low daily dose of cyclophosphamide, and her progression-free survival was 65 months without side effects. She was well during the chemotherapy and lived a normal working and social life [44].

Preclinical data showed an improved outcome for combining metronomic cyclophosphamide with bevacizumab in various tumor models. Based on this, a phase II prospective clinical trial evaluated this combination in recurrent ovarian cancer [45]. Patients with measurable disease and prior treatment with a platinum-containing regimen were eligible. Up to two different regimens for recurrent disease were allowed. Treatment consisted of bevacizumab 10 mg/kg intravenously every 2 weeks and oral cyclophosphamide 50 mg/day. The primary end point was progression-free survival at 6 months. Seventy patients were enrolled. The median number of prior chemotherapy treatments was 2. The probability of being alive and progression-free at 6 months was 56 % (6 % SE). A partial response was achieved in 17 patients (24 %). Median time to progression and survival were 7.2 and 16.9 months, respectively. This data suggested that the combination of metronomic cyclophosphamide and bevacizumab was associated with impressive activity and a very favorable toxicity profile in recurrent ovarian cancer. Subsequent retrospective and prospective studies have confirmed these findings [46–48].

Table 14.2 Phase II clinical trials of bevacizumab alone and metronomic cyclophosphamide alone or in combination in recurrent ovarian cancer

Study	Design	Prior treatment	Grade 3/4 toxicities (%)	Activity
Burger et al. [49]	Phase II single agent *N* = 62	1–2 lines 42 % platinum resistant	Hypertension 11 Thrombosis 3 GI perforation 0 (all grades)	RR = 21 % Estimated 6 month PFS = 40 %
Cannistra et al. [50]	Phase II single agent *N* = 44	2–3 lines 87 % platinum resistant	Hypertension 9 Thrombosis 7 GI perforation 11 (all grades)	RR = 16 % Estimated 6-month PFS = 24 %
Garcia et al. [45]	Phase II bevacizumab plus metronomic cyclophosphamide *N* = 70	1–3 lines 40 % platinum resistant	Hypertension 16 Thrombosis 5 GI perforation 6 (all grades)	RR = 24 % 6 month PFS = 56 %
Kummar et al. [51]	Phase II randomized metronomic cyclophosphamide +/− veliparib *N* = 74	1–4 lines	Grade ≥2 toxicities (%) Lymphopenia 6 Mucositis 1	RR = 13 % 6-month PFS not stated

A limitation of this study is the lack of a control arm. Therefore, the individual contribution of bevacizumab and cyclophosphamide is unknown. The activity of single-agent bevacizumab in recurrent ovarian cancer is well defined, while until recently the activity of single-agent cyclophosphamide was unknown until recently.

Two phase II clinical trials evaluated the activity of single-agent bevacizumab in recurrent ovarian cancer [49, 50] and reported response rates of 21 and 16 % and estimated 6-month PFS of 40 and 24 %, respectively. Recently, the results of a phase II randomized trial of metronomic cyclophosphamide alone or in combination with veliparib were reported in abstract form [51]. Seventy-four patients were enrolled and thirty-six were randomized to cyclophosphamide alone. Median number of prior therapies was 4 [range 1–4]. The response rate to single-agent cyclophosphamide was 13 %. Time to progression or overall survival was not reported. Treatment with oral cyclophosphamide was well tolerated as the only grade 2 or higher toxicities reported were lymphopenia and mucositis observed in 2 and 1 patient respectively.

Table 14.2 summarizes the results of these studies. Within the limitation of cross comparison among trials, the available data suggests that the combination of bevacizumab and metronomic chemotherapy seems to be more active than single-agent bevacizumab or metronomic cyclophosphamide as the response rate is slightly higher, but more importantly the 6-month progression-free survival is among the highest ever reported for recurrent ovarian cancer. These studies also suggest that metronomic cyclophosphamide administered as single agent has a very favorable toxicity profile and activity comparable to that of bevacizumab in this setting.

14.5 Topotecan

Tumor angiogenesis is regulated by a balance of stimulatory and inhibitory factors modulated by both the tumor cells and the tumor microenvironment [52]. Among the stimulatory factors, hypoxia inducible factor [Hif] plays a critical role in hypoxia-mediated angiogenesis [53]. Topotecan, a semisynthetic analogue of camptothecin, is a potent topoisomerase I inhibitor [54] and is currently FDA approved in the United States for the treatment of recurrent ovarian cancer at a dose of 1.5 mg/m^2 daily for 5 days, given as a 30-minute infusion and repeated every 21 days. Along with its cytotoxic effects, topotecan has been suggested to possess potent antiangiogenic properties and is a Hif-1 antagonist [55].

An in vitro and in vivo experiment by Merrit et al. dose-finding and therapy experiments with oral metronomic topotecan was performed in an orthotopic model of advanced ovarian cancer. Tumor vascularity, proliferation, and apoptosis were examined among treatment arms, and in vitro experiments including MTT and Western blot analysis were performed to identify specific antiangiogenic mechanisms of topotecan. The results revealed that compared to controls, metronomic (0.5, 1.0 and 1.5 mg/kg; daily) and maximum tolerated therapy (MTD; 7.5 and 15 mg/kg; weekly) dosing regimens reduced tumor growth in dose-finding experiments, but significant morbidity and mortality were observed with higher doses. Metronomic and MTD topotecan therapy significantly reduced tumor growth in both HeyA8 and SKOV3ip1 models: 41–74 % (metronomic) and 64–86 % (MTD dosing) ($P<0.05$ for both regiments compared to controls). Compared to controls, the greatest reduction in tumor MVD was noted with metronomic dosing (32–33 %; $P<0.01$). Tumor cell proliferation was reduced ($P<0.001$ vs. controls) and apoptosis increased in all treatment arms ($P<0.01$ vs. controls) for both dosing regimens. Endothelial cells demonstrated a significantly higher sensitivity to topotecan using metronomic dosing versus MTD in vitro. Pro-angiogenic regulators Hif-1α and VEGF levels were reduced in vitro [HeyA8 and SKOV3ip1] with topotecan independent of proteasome degradation and topoisomerase I [56].

In addition, Hashimoto et al. developed a preclinical model of advanced human ovarian cancer and tested various low-dose metronomic chemotherapy regimens [57]. Clones of the SKOV-3 human ovarian carcinoma cell line expressing a secretable beta-subunit of human choriogonadotropic (beta-hCG) protein and firefly luciferase were generated and evaluated for growth after orthotopic (i.p.) injection into severe combined immunodeficient mice; a highly aggressive clone, SKOV-3-13, was selected for further study. Mice were treated beginning 10–14 days after injection of cells when evidence of carcinomatosis-like disease in the peritoneum was established as assessed by imaging analysis. Chemotherapy drugs tested for initial experiments included oral cyclophosphamide or topotecan and intraperitoneal irinotecan, topotecan, cisplatin, or paclitaxel given alone or in doublet combinations. In this model, metronomic cyclophosphamide had no antitumor activity, whereas metronomic irinotecan and topotecan had potent activity.

Clinical trials have evaluated the activity of topotecan administered as a protracted low-dose continuous infusion [58–60]. In these studies, topotecan was

administered at a dose of 0.4 mg/m^2/day for 14–21 days. Response rates of 8–35 % were reported, comparable to those achieved with the approved regimen. Neutropenia appears to be significantly lower with continuous infusion, while other toxicities, including anemia and thrombocytopenia, are comparable. However, despite its encouraging activity and favorable toxicity profile, continuous infusion of topotecan is not routinely used probably in part due to the inconveniences and limitations required to administer protracted infusions in daily clinical practice.

With the development of an oral formulation of topotecan, Tillmans et al. performed a phase I trial to determine the MTD of daily oral topotecan [61]. Dose levels of 0.25, 0.50, 0.75, 1.00, and 1.25 mg were studied. Sixteen heavily pretreated patients with various solid tumors were enrolled, with an average of four prior regimens. Mean cycles received on protocol were two (range 1–6). The topotecan Cmax increased linearly with dose, and the median (range) Tmax was 2 h (1–7). The DLT was reached at 1.25 mg (two patients had Gr.3 GI toxicities). Two patients (14 % response) had stable disease (one patient with a minor response and one patient with cervical cancer has stable disease for 7 months on therapy after multiple recurrences on prior regimens). The remaining patients had disease progression. The MTD for phase II evaluation was defined at 1.0 mg daily. The authors concluded that this 28-day cycle was well tolerated at a MTD dose of 1 mg orally daily.

Based on the activity observed with metronomic irinotecan and topotecan, Hashitmoto also evaluated the combination of orally administered metronomic topotecan in combination with pazopanib, a potent tyrosine kinase inhibitor which targets VEGF and platelet-derived growth factor (PDGF) receptors [57]. Pazopanib as a single agent had modest efficacy. However, the high activity of topotecan was significantly enhanced with the addition of pazopanib, with 100 % prolonged survival for the drug combination, after 6 months of continuous therapy. Similarly, findings were reported by Merritt [62].

These findings lead to a phase clinical trial evaluating the combination of metronomic oral topotecan and pazopanib [63, 64]. Twenty-five patients with gynecological tumors were enrolled. The recommended dose for phase I trials was determined to be topotecan 0.25 mg/day with pazopanib 600 mg/day. There were no grade 4 toxicities, and the most common grade 3 toxicities were neutropenia, anemia, and increased transaminases seen in 12, 8, and 8 % of patients, respectively. An overall response rate of 36 % was observed. Twenty-one patients were evaluable for pharmacokinetic studies. No significant drug interactions were observed.

Acknowledgement We want to acknowledge Salomon Ramirez for his invaluable technical support, drafting and revising of the manuscript

References

1. National Cancer Institute. SEER stat fact sheets: ovary [internet]. National Cancer Institute, Bethesda. Available from: http://seer.cancer.gov/statfacts/html/ovary.html. Cited Oct 2013
2. Cannistra SA (2004) Cancer of the ovary. N Engl J Med 351:2519–2529

3. Pfisterer J, Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ et al (2006) Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 24:4699–4707. doi:10.1200/JCO.2006.06.0913
4. Parmar M, Ledermann J, Colombo N, du Bois A, Delaloye J, Kristensen G et al (2003) Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 361:2099–2106
5. Bamias A, Bamia C, Zaqouri F, Kostouros E et al (2013) Improved survival trends in platinum-resistant patients with advanced ovarian, fallopian or peritoneal cancer treated with first-line paclitaxel/platinum chemotherapy: the impact of novel agents. Oncology 84(3):158–165. doi:10.1159/000341366, Epub 2012 Dec 28
6. Lortholary A, Largillier R, Weber B, Gladieff L (2012) Weekly paclitaxel as a single agent or in combination with carboplatin or weekly topotecan in patients with resistant ovarian cancer: the CARTAXHY randomized phase II trial from Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO). Ann Oncol 23(2):346–352. doi:10.1093/annonc/mdr149, Epub 2011 May 11
7. Bolis G, Parazzini F, Scarfone G et al (1999) Paclitaxel vs epidoxorubicin plus paclitaxel as second-line therapy for platinum-refractory and -resistant ovarian cancer. Gynecol Oncol 72:60–64
8. Monk BJ, Herzog TJ, Kaye SB et al (2010) Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol 28:3107–3114
9. Chabner BA, Roberts TG Jr (2005) Timeline: chemotherapy and the war on cancer. Nat Rev Cancer 5(1):65
10. Gasparini G (2001) Metronomic scheduling: the future of chemotherapy? Lancet Oncol 2:733–740
11. Kerbel RS, Kamen BA (2004) The anti-angiogenic basis of metronomic chemotherapy. Nat Rev Cancer 4:423–436
12. Scharovsky OG, Mainetti LE, Rozados VR (2009) Metronomic chemotherapy: changing the paradigm that more is better. Curr Oncol 16:7–15
13. Hanahan D, Bergers G, Bergsland E (2000) Less is more regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. J Clin Invest 105:1045–1047
14. Su WH, Ho TY, Li YT, Lu CH, Lee WL, Wang PH (2012) Metronomic therapy for gynecologic cancers. Taiwan J Obstet Gynecol 51:167–178
15. Lien K, Georgsdottir S, Sivanathan L, Chan K, Emmenegger U (2013) Low-dose metronomic chemotherapy: a systematic literature analysis. Eur J Cancer 49(16):3387–3395
16. Ge Y, Domschke C, Stoiber N, Schott S, Heil J, Rom J, Blumenstein M, Thum J, Sohn C, Schneeweiss A et al (2012) Metronomic cyclophosphamide treatment in metastasized breast cancer patients: immunological effects and clinical outcome. Cancer Immunol Immunother 61(3):353–362, Epub 14 Sep 2011
17. Miller KD, Sweeney CJ, Sledge GW Jr (2001) Redefining the target: chemotherapeutics as antiangiogenics. J Clin Oncol 19(4):1195–1206
18. Browder T et al (2000) Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res 60:1878–1886
19. Bell J, Brady MF, Young RC, Lage J, Walker JL, Look KY, Rose GS, Spirtos NM (2006) Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 102(3):432–439, Epub 24 Jul 2006
20. Bookman MA, Brady MF, McGuire WP, Harper PG et al (2009) Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. J Clin Oncol 27(9):1419–1425
21. Markman M, Bundy BN, Alberts DS, Fowler JM (2001) Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an

intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 19(4):1001–1007
22. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R et al (2006) Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 354(1):34–43
23. Alberts DS, Liu PY, Hannigan EV, O'Toole R (1996) Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 335(26):1950–1955
24. Gaillard S, Armstrong D (2011) Intraperitoneal chemotherapy for advanced epithelial ovarian cancer: many questions, much promise…. Oncology (Williston Park) 25(2):176, 178, 180
25. Katsumata N, Yasuda M, Takahashi F, Isonishi S (2009) Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 374(9698):1331–1338. doi:10.1016/S0140-6736(09)61157-0, Epub 2009 Sep 18
26. Burger RA, Brady MF, Bookman MA, Fleming GF (2011) Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 365(26):2473–2483
27. Perren TJ, Swart AM, Pfisterer J, Ledermann JA (2011) A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 365(26):2484–2496
28. Markman M, Liu PY, Wilczynski S, Monk B (2003) Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. J Clin Oncol 21(13):2460–2465
29. Mannel RS, Brady MF, Kohn EC, Hanjani P (2011) A randomized phase III trial of IV carboplatin and paclitaxel×3 courses followed by observation versus weekly maintenance low-dose paclitaxel in patients with early-stage ovarian carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol 122(1):89–94
30. Morgan R, Alvarez R, Armstrong D, Burger R et al (2013) Ovarian cancer version 2.2013. J Natl Compr Canc Netw 11(10):1199–1209
31. Kikuchi Y, Kita T, Takano M, Kudoh K, Yamamoto K (2005) Treatment options in the management of ovarian cancer. Expert Opin Pharmacother 6(5):743–754
32. Lopes NM, Adams EF, Pitts TW, Bhuyan BK (1993) Cell kinetics and cell cycles effects of Taxol on human and hamster ovarian cell lines. Cancer Chemother Pharmacol 432:235–242
33. Georgiadis MS, Russel E, Gazdar AF, Johnson BE (1997) Paclitaxel cytotoxicity against human lung cancer cell lines increases with prolonged exposure duration. Clin Cancer Res 3:449–454
34. Yamamoto K, Kikuchi Y, Kudoh K, Nagata I (2000) Modulation of cisplatin sensitivity by Taxol in cisplatin-sensitive and –resistant human ovarian carcinoma cell lines. J Cancer Res Clin Oncol 126:168–172
35. Markman M, Hall J, Spitz D, Weiner S (2002) Phase II trial of weekly single-agent paclitaxel in platinum/paclitaxel-refractory ovarian cancer. J Clin Oncol 20(9):2365–2369
36. Markman M, Blessing J, Rubin SC, Connor J et al (2006) Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol 101(3):436–440, Epub 2 Dec 2005
37. Perez EA, Vogel CL, Irwin DH et al (2001) Multicenter Phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 19:4216–4223
38. Socinski MA, Schell MJ, Bakri K et al (2002) Second-line, low-dose, weekly paclitaxel in patients with stage IIIB/IVnon-small cell lung carcinoma who fail first line chemotherapy with carboplatin plus paclitaxel. Cancer 95:1265–1273
39. Jaaback K, Johnson N, Lawrie TA (2011) Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database Syst Rev 11:1–59
40. National Cancer Institute. Issues clinical announcement for preferred method of treatment for advanced ovarian cancer. National Cancer Institute, Bethesda. Available on http://www.cancer.gov/cancertopics/pdq/treatment/ovarianepithelial/HealthProfessional. Cited 4 Jan 2006

41. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A et al (2013) Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 24(Suppl 6):vi24–vi32
42. Browder T, Butterfield CE, Kraling BM, Shi B, Marshall B, O'Reilly MS et al (2000) Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res 60:1878e86
43. Colleoni M, Rocca A, Sandri MT, Zorzino L, Masci G, Nole F et al (2002) Low dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels. Ann Oncol 13:73–80
44. Samaritani R, Corrado G, Vizza E, Sbiroli C (2007) Cyclophosphamide "metronomic" chemotherapy for palliative treatment of a young patient with advanced epithelial ovarian cancer. BMC Cancer 7:65
45. Garcia AA, Hirte H, Fleming G, Yang D, Tsao-Wei DD, Roman L et al (2007) Phase II clinical trial of bevacizumab and low dose metronomic oral cyclophosphamide in recurrent ovarian cancer. A study of the California, Chicago and Princess Margaret Hospital Phase II Consortia. J Clin Oncol 26:76–82
46. Sánchez-Muñoz A, Mendiola C, Pérez-Ruiz E, Rodríguez-Sánchez CA, Jurado JM et al (2010) Bevacizumab plus low dose metronomic oral cyclophosphamide in heavily pretreated patients with recurrent ovarian cancer. Oncology 79(1–2):98–104. doi:10.1159/000320602, Epub 15 Nov 2010
47. Barber EL, Zsiros E, Lurain JR, Rademaker A, Schink JC, Neubauer NL (2013) The combination of intravenous bevacizumab and metronomic oral cyclophosphamide is an effective regimen for platinum-resistant recurrent ovarian cancer. J Gynecol Oncol 24(3):258–264. doi:10.3802/jgo.2013.24.3.258, Epub 2013 Jul 4
48. Chura JC, Van Iseghem K, Downs LS Jr, Carson LF, Judson PL (2007) Bevacizumab plus cyclophosphamide in heavily pretreated patients with recurrent ovarian cancer. Gynecol Oncol 107(2):326–330, Epub 15 Aug 2007
49. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI (2007) Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 25(33):5165–5171, (2007) J Clin Oncol 25(33):5180–6. (2008) Erratum in: J Clin Oncol 26(10):1773
50. Cannistra SA, Matulonis UA, Penson RT, Hambleton J et al (2007) Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 25(33):5180–5186, (2008) Erratum in: J Clin Oncol 26(10):1773
51. Kummar S, Oza AM, Fleming GF et al (2012) Randomized trial of oral cyclophosphamide (C) with or without veliparib (V), an oral poly (ADP-ribose) polymerase (PARP) inhibitor, in patients with recurrent BRCA-positive ovarian, or primary peritoneal or high-grade serous ovarian carcinoma. J Clin Oncol 30(Suppl): abstr 5020
52. Carmeliet P, Jain RK (2000) Angiogenesis in cancer and other diseases. Nature 407:249–257
53. Pugh CW, Ratcliffe PJ (2003) Regulation of angiogenesis by hypoxia: role of the HIF system. Nat Med 9:677–684
54. Pommier Y (2006) Topoisomerase I, inhibitors: camptothecins and beyond. Nat Rev Cancer 6:789–802
55. Clements MK, Jones CB, Cumming M, Daoud SS (1999) Antiangiogenic potential of camptothecin and topotecan. Cancer Chemother Pharmacol 44:411–416
56. Merritt W, Danes C, Shahzad M, Lin Y et al (2009) Anti-angiogenic properties of metronomic topotecan in ovarian carcinoma. Cancer Biol Ther 8(16):1596–1603
57. Hashimoto K, Man S, Xu P, Cruz-Munoz W, Tang T et al (2010) Potent preclinical impact of metronomic low-dose oral topotecan combined with the antiangiogenic drug pazopanib for the treatment of ovarian cancer. Mol Cancer Ther 9(4):996–1006
58. Denschlag D, Watermann D, Hörig K, Kissel C et al (2004) Topotecan as a continuous infusion over 14 days in recurrent ovarian cancer patients. Anticancer Res 24(2C):1267–1269
59. Hochster H, Wadler S, Runowicz C, Liebes L et al (1999) Activity and pharmacodynamics of 21-Day topotecan infusion in patients with ovarian cancer previously treated with

platinum-based chemotherapy. New York Gynecologic Oncology Group. J Clin Oncol 17(8):2553–2561
60. Gore M, Rustin G, Schüller J, Lane SR et al (2001) Topotecan given as a 21-day infusion in the treatment of advanced ovarian cancer. Br J Cancer 84(8):1043–1046
61. Tillmanns TD, Buller R, Stewart CF et al (2008) Daily oral topotecan: utilization of a metronomic dosing schedule to treat recurrent or persistent solid tumors. J Clin Oncol 26(15S):257 (20 May Supplement)
62. Merritt WM, Nick AM, Carroll AR, Lu C et al (2010) Bridging the gap between cytotoxic and biologic therapy with metronomic topotecan and pazopanib in ovarian cancer. Mol Cancer Ther 9(4):985–995
63. Tillmanns T, Reed M, Privett M, Johns A et al (2012) Phase I trial of metronomic oral topotecan in combination with pazopanib. J Clin Oncol 30 (suppl; abstr 5014)
64. Turner DC, Tillmanns TD, Harstead KE, Throm SL, Stewart CF (2013) Combination metronomic oral topotecan and pazopanib: a pharmacokinetic study in patients with gynecological cancer. Anticancer Res 33(9):3823–3829