3 *vs* Group 4, log rank). Figure 3 shows the combined survival of Group 4 and Group 3 and that of Group 2 and Group 1. Patients with three or all four favourable factors (Group 3/4) ($n=31$) had significantly better survival compared with those with less than three favourable factors (Group 1/2) ($n=13$) (median and 5-year survival; 47 months and 45.9% *vs* 20 months and 0%, $P<0.001$).

Survival of patients determined by the number of favourable prognostic factors and SCS outcome

Patients with three or all four favourable prognostic factors (Group 3/4) had better survival when complete surgical resection was achieved at the time of SCS ($n=23$) (64 months in median survival, 53.8% in 5-year survival). However, even when SCS left residual tumours, survival of the Group 3/4 patients ($n=8$) was fairly good (40 months in median survival, 25% in 5-year survival). On the other hand, Group 1/2 patients had poorer survival both in completely resected cases ($n=3$) and in incompletely resected cases ($n=10$) (23 and 18 months in median survival, and 0 and 0% in 5-year survival) (Figure 4).

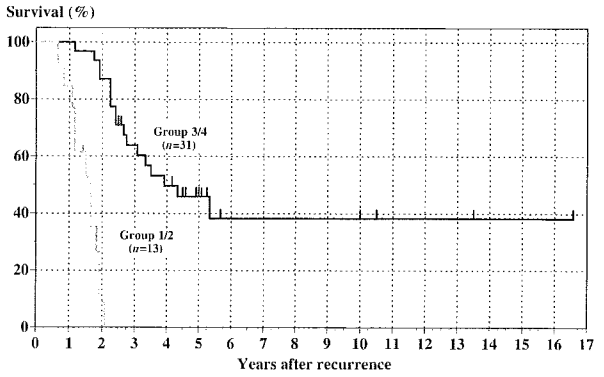

Figure 3 Comparison in survival between patients having one or two favourable prognostic factors (Group 1/2) and three or four favourable factors (Group 3/4). Survival of patients in Group 3/4 and Group 1/2 is shown as a solid black or solid grey line, respectively. Patients in Group 3/4 had significantly better survival compared with patients in Group 1/2 ($P<0.001$, log rank).

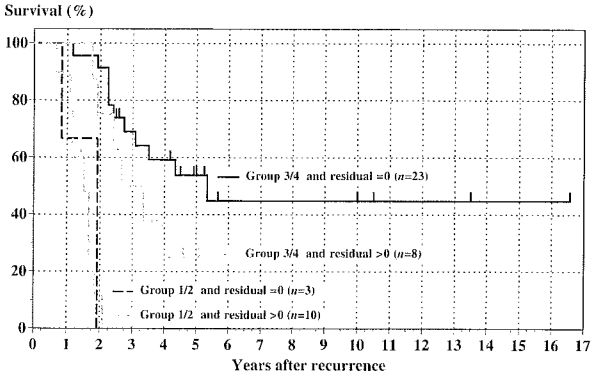

Figure 4 Survival in relation to SCS outcome and number of favourable prognostic factors. Survival of patients in Group 3/4 are shown as solid lines. Solid black line and solid grey line show the survival of patients with no residual tumour and residual tumour at SCS, respectively. Survival of patients in Group 1/2 are shown as dotted lines. Dotted black line and dotted grey line show the survival of patients with no residual tumour and any residual tumour at SCS, respectively.

DISCUSSION

We achieved surgical removal of all visible tumours in 59.1% of patients at the time of SCS. Residual tumours <1 or $\geqslant 1$ cm in diameter were present in 25.0 and 15.9%, respectively. In line with previous reports, removal of all visible tumours at SCS contributed to long-term survival (Figure 2). The rate of complete resection (59.1%) in our series was a little lower than the rates reported by Eisenkop *et al* (2000), Landoni *et al* (1998) and Cormio *et al* (1999). However, in Landoni's study, the subjects were restricted to those patients who were sensitive to first-line chemotherapy and chemotherapy before SCS. Cormio *et al* also restricted the subjects to patients with apparently isolated and resectable tumours and without ascites. Our criteria for patient selection were similar to those of Eisenkop *et al*, and their subjects were patients with DFI >6 months and without liver metastases. They achieved an 82% complete resection rate by using argon beam laser to remove disseminated cancer foci and reported 44 months in median survival and approximately 35% in 5-year survival in the completely resected cases. In our experience, median survival and 5-year survival in completely resected cases were 52 months and 47.6%, respectively, being much better than previous reports. Our rate of optimal cytoreduction, 84.1% (if defined as residual tumour <1 cm), was similar to the rate of complete resection in Eisenkop's report. In our series, optimally resected cases had 40 months in median survival and 38.6% in 5-year survival (figure not shown), in keeping with the survival of completely resected cases in Eisenkop's study. These findings suggest that the debulking efforts performed at SCS in our cases are comparable to those of previous reports.

Univariate analyses revealed that three factors during primary treatment (peritoneal spread, aortic lymph node metastasis, FIGO stage) and five factors at recurrence (DFI, liver metastasis, number of tumours, size of maximum tumour, SCS outcome) were significantly related to overall survival after recurrence. In the multivariate analysis excluding SCS outcome, the significance of all the three factors during primary treatment disappeared. Four factors determined at recurrence, that is, DFI, presence of liver metastasis, number of tumours and size of maximum tumour, were revealed to be independent prognostic factors.

DFI is the most important prognostic factor after recurrence, as described in many previous reports. In most studies, the cutoff period of DFI was set to 12 months. Two cutoff periods were set in Eisenkop's study (Eisenkop *et al*, 2000) (12 and 36 months) and in Tay's study (Tay *et al*, 2002) (12 and 24 months), and patients were divided into three groups. Although we also analysed our patients with DFI >12 months using cutoff periods such as 24 and 36 months, there were no significant differences between patients with and without DFI >24 or 36 months (data not shown). Recently, Zang *et al* (2004) performed SCS even in patients with DFI of 3 months and reported negative influence of DFI on overall survival. However, their follow-up period was only 16 months. This might be too short to detect a statistical difference.

Size of maximum tumour was also identified by Eisenkop *et al* (2000) as an independent prognostic factor. Eisenkop *et al* used 10 cm as the cutoff size, whereas we used 6 cm. The difference may be due to our earlier detection of recurrent tumours by using ultrasonography or CT scan within a 3-month interval. In our cases, there were only two patients in whom maximum tumour size exceeded 10 cm in diameter. At all events, tumour size seems to be an important factor reflecting biological aggressiveness of recurrent tumours.

The number of recurrent tumours has not been previously highlighted as a prognostic determinant. One reason is that some studies restricted the subjects for SCS to patients with isolated tumours or a solitary tumour (Cormio *et al*, 1999; Munkarah *et al*, 2001; Scarabelli *et al*, 2001). Another possible reason is that Eisenkop *et al* (2000) and Tay *et al* (2002) did not analyse the

number of recurrent tumours as a factor influencing survival, although they pointed out that this factor may influence SCS outcome. In concordance with our results, Zang *et al* (2004) reported that the number of recurrent tumours influenced both overall survival and SCS outcome.

The current study revealed that liver metastasis is another important prognostic determinant. Vaccarello *et al* (1995) examined the relationship between site of recurrence and survival, and reported that liver metastasis had a negative influence on survival. In most studies, patients with liver metastasis were excluded from subjects for SCS. In our series, two patients with solitary liver metastasis were included: one patient underwent hepatic resection and the other patient did not undergo hepatic resection because of the presence of unresectable metastatic portal lymph nodes. They did not achieve good survival (20 and 14 months, respectively).

From the results of the multivariate analysis, we propose the following criteria for patient selection for SCS. Patients with recurrent ovarian cancer should be considered as ideal candidates for SCS when they have three or all of the following four factors at recurrence: (1) DFI >12 months, (2) no liver metastasis, (3) a solitary tumour and (4) tumour size <6 cm. Considering our original patient selection, we should propose exclusion criteria including (1) age at recurrence $\geqslant 75$ years, (2) PS 3 or 4 just before SCS and (3) progressive disease during presurgical chemotherapy, if undertaken. Although we used intraoperative findings for the number and size of tumours, size of maximum tumour was consistent between intraoperative findings and imaging in available cases. Therefore, we can accurately evaluate all these factors, except the number of tumours, before SCS. As for the number of tumours, ultrasonography or CT scan before SCS cannot always identify multiple peritoneal disseminated tumours. When the patient meets the criteria for SCS preoperatively, it is recommended to decide whether SCS should be accomplished after reconfirming the criteria at the time of laparotomy.

In the previous studies, several prognostic factors were shown to have significant correlation with overall survival of the patients. However, these factors were obtained from SCS in selected patients in most of the previous studies. In addition, how to use several significant prognostic factors to select good candidates for SCS was not fully analysed. To our knowledge, generally accepted or recommended selection criteria are 'patients with longer DFI' (Bristow *et al*, 1996; Roberts, 1996; Rose, 2000; Sijmons and Heintz, 2000). Thus, it was sometimes difficult to decide whether or not SCS should be performed in patients who have some favourable factors and a few unfavourable factors. We believe that our selection criteria for SCS should be helpful in deciding whether SCS should be performed.

In conclusion, our data suggest that patients with three or all four of the above-mentioned favourable factors are ideal candidates for SCS, and that the final decision should be made at laparotomy in borderline cases. It seems that SCS has a large impact on survival of patients with recurrent ovarian cancer when the patients are selected by the new criteria (47 months in median survival and 45.9% in 5-year survival). However, these patients were likely to have good sensitivity to chemotherapy, because they had DFI >6 months. In a recent trial of recurrent ovarian cancer with DFI >6 months, patients who received platinum-based chemotherapy with or without paclitaxel had a favourable prognosis: 29 and 24 months in median survival and around 20% in 5-year survival, respectively (Parmar *et al*, 2003). Although patients undergoing SCS using the new criteria of patient selection seem to have much better survival than patients receiving chemotherapy alone, our study was retrospective and noncomparative, and our data were based on a relatively small number of strictly selected patients. To provide solid evidence for the therapeutic benefit of SCS and to find better selection criteria for the surgery, further studies including randomised controlled studies are required.

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Treatment options in the management of ovarian cancer

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The standard regimen used as primary chemotherapy of ovarian cancer is combination chemotherapy using paclitaxel and carboplatin. The main objective of first-line chemotherapy is to induce complete response. Although most cases respond to the initial chemotherapy, many cases relapse within 3 years. Such relapsed and persistent cases become resistant to first-line chemotherapy and require second-line chemotherapy. Objectives of such a second-line chemotherapy are to obtain disease palliation to cease disease progression. Meanwhile, consolidation or maintenance chemotherapy may be added to prevent or inhibit disease relapse for patients with advanced disease after induction of complete remission by a primary chemotherapy. When the unresectable tumour is presumed by primary surgery, neoadjuvant chemotherapy may be selected. Recently, conventional cytotoxic anticancer drugs containing paclitaxel have been shown to be capable of inhibiting angiogenesis. The notion of 'redefining' chemotherapeutic drugs has been recognised; thus, continuous low-dose chemotherapy – so-called metronomic chemotherapy – has been approved as a new concept. Many new molecular-targeted therapies became available for clinical cancer therapy. The explosion of new molecular targets and the development and application of many powerful technologies should accelerate the discovery of innovative molecular therapeutics. Understanding the molecular mechanisms will help to clarify the pathways in ovarian cancer development and help to identify new therapeutic and diagnostic targets. These are exciting times for new drug development and the treatment of cancer. Cautious optimism should prevail for all investigators involved in translating these exciting new biological findings into new pharmacological agents for treatment of cancer.

Keywords: chemotherapy, ovarian cancer

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1. Introduction

For centuries, surgery was considered the only curative treatment for cancer. Likewise, radiation therapy offered some patients a possible cure for localised cancers. However, once the disease had spread from its original site of origin, the patient was deemed inoperable and, therefore, incurable. The first drug used for cancer treatment was a derivative of mustard gas [1]. In 1948, Farber and associates [2] reported on the use of folate antagonists for the treatment of childhood leukaemia. Since that time, > 100 pharmacological agents have been introduced for that treatment of cancer. Combining agents with different mechanisms of action and nonoverlapping toxicities is now considered the most acceptable approach to the eradication of disseminated cancers.

Ovarian cancer is the fifth leading cause of cancer death in women in the US, with an estimated 23,300 cases diagnosed and 13,900 deaths in 2002 [3]. Improvements in the management of ovarian cancer have resulted in increased 5-year

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survival rates to > 50% over the period of 1992 – 1997 [3]. Data from Europe have demonstrated increases in 5-year survival that vary from 26% for Eastern Europe to 42% for Northern Europe [4]. However, the prognosis for patients with ovarian cancer remains poor. Up to 75% of patients are diagnosed in the advanced stage and many require chemotherapy after cytoreductive surgery [5]. Although 10 – 15% of patients maintain a response to standard first-line cisplatin/paclitaxel chemotherapy, most patients eventually relapse [6]. The goals of treating advanced recurrent ovarian cancer are mainly palliative, attempting to prolong life and control disease-related symptoms, while minimising treatment-related toxicities and maximising health-relapsed quality of life.

Some significant advances in clinical oncology using standard- or high-dose regimens have been achieved, but such gains seem to have reached a plateau over the past two decades, in part as a result of drug resistance. The shift to alternative targets within the tumour and the use of these targets for the subset of patients who, either because of intrinsic or acquired resistance, are not likely to respond to standard therapy holds promise. The results of Colleoni *et al.* [7] may herald a gradual shift from standard maximum tolerated dose (MTD) or high-dose chemotherapy, to, at least in the chemoresistant population, induction of antiangiogenesis by low-dose chemotherapy. At present, most of the new receptor blocking agents such as gefitinib (ZD-1839/Iressa®, AstraZeneca Pharmaceuticals LP) or cetuximab (C-225/Erbitux™, ImClone Systems Incorporated), as well as antiangiogenic drug (e.g., bevacizumab/Avastin™ [Genentech, Inc.]: the humanised monoclonal antibody to vascular endothelial growth factor [VEGF]), are used with standard chemotherapy regimens, which negates their superior safety profiles. As the cancer patient population ages, should these combinations also be evaluated in the setting of low-dose, frequent, continuous chemotherapy? The time may come when the term 'side effect' for chemotherapeutic drugs not only loses its negative connotations, but takes on a new, and positive, meaning.

2. Induction chemotherapy (primary chemotherapy)

Surgery followed by systemic chemotherapy is the current standard treatment modality for epithelial ovarian cancer, particularly when diagnosis is made at an advanced stage [8,9]. The combination of paclitaxel and cisplatin replaced schemes without paclitaxel after it was shown in the Gynecologic Oncology Group Trial 111 [10] and in a subsequent confirmatory trial [11] that it was more effective than the combination of cyclophosphamide and cisplatin. In fact, paclitaxel combined with carboplatin is considered the standard first-line chemotherapy regimen worldwide because of its more favourable toxicity profile as compared with paclitaxel and cisplatin [12-14]. Surgery and first-line systemic chemotherapy induce complete and partial response in ≤ 80% of patients, with a pathological complete remission rate of ~ 25% [10,11]. Unfortunately, recurrences occur in the majority of patients, and only 20 – 40% survive after a 5-year follow-up period, with survival being substantially dependant on the initial International Federation of Gynecology and Obstetrics stage [15].

Important questions about the clinical value of platinum/taxane combinations have been raised by the results of the large International Collaborative Ovarian Neoplasm Group 3 study involving 2074 ovarian cancer patients. The data from this trial suggest that there was no benefit, in terms of either progression-free or overall survival, from the use of paclitaxel/carboplatin compared with carboplatin alone or cyclophosphamide/doxorubicin/cisplatin [16]. Furthermore, the incidences of alopecia, fever and sensory neuropathy were significantly higher in the taxane treatment arm compared with carboplatin alone. The SCOTROC Randomised trial in Ovarian Cancer has compared the use of two different taxane preparations in combination with platinum to determine whether there were any differences in efficacy or tolerability. A total of 1077 patients were randomised to receive either docetaxel/carboplatin or paclitaxel/carboplatin [17]. The results indicate that there was no significant difference between these regimens in terms of either median progression-free survival (15.1 months for docetaxel/carboplatin versus 15.4 months for paclitaxel/carboplatin) or overall survival at 18 months (73.5 versus 76.6%, respectively). However, there were some differences between the two treatment groups regarding their tolerability profiles, with paclitaxel associated with significantly greater neurotoxicity, arthralgia/myalgia and weakness in the legs or arms compared with docetaxel. Nevertheless, global quality of life parameters based on the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire were comparable in both treatment arms. These data suggest that individual patients might benefit from the use of one or the other taxane, depending on their predisposition to adverse effects such as neuropathy.

Recent studies assessing the effects of the addition of epirubicin to platinum/taxane have shown a higher response rate among patients in the epirubicin treatment arm compared with those receiving platinum/taxane alone, although there was also a higher incidence of toxicity in these patients [18]. A number of newer chemotherapeutic agents are being assessed for a potential role in first-line treatment regimens for ovarian cancer, including gemcitabine, pegylated liposomal doxorubicin, irinotecan, oxaliplatin and topotecan. Of these agents, topotecan has been extensively studied using a variety of different treatment strategies. The mechanism of action of topotecan (inhibition of topoisomerase I) is different from that of paclitaxel, with no overlap, and synergy has been demonstrated in *in vitro* tumour models with paclitaxel and platinum [19,20]. Topotecan has also shown activity in platinum- and paclitaxel-resistant tumours, and there is an absence of cross-resistance with paclitaxel [21]. Likewise, in Japan, irinotecan (but not topotecan) is frequently used for platinum- and paclitaxel-resistant tumours. Both clear cell carcinoma and mucinous cystadenocarcinoma in advanced stages are poorly responsive

to platinum- or taxane-based chemotherapy [22-24]. In addition, the authors of this review have examined response rates to standard regimens according to histological type. The response rate of clear cell carcinoma was significantly lower (showing 11.1%), compared with 72.5% of serous cystadenocarcinoma [22]. In patients with > 2 cm residual tumour the response rate to cyclophosphamide/adriamycin/cisplatin (CAP) regimen was also lower in mucinous cystadenocarcinoma and clear cell carcinoma compared with serous cystadenocarcinoma and endometrioid adenocarcinoma. However, when etoposide/cisplatin and irinotecan/cisplatin were used to treat mucinous cystadenocarcinoma and clear cell adenocarcinoma, respectively, significant response rates (33 and 50%, respectively) were obtained [25]. The standard regimen for clear cell adenocarcinoma and/or mucinous adenocarcinoma should be evaluated by independent trials. Thus, this group are using a standard regimen (paclitaxel/carboplatin) to treat serous cystadenocarcinoma and endometrioid adenocarcinoma as a first-line chemotherapy, whereas combination chemotherapy using etoposide and cisplatin to treat mucinous cystadenocarcinoma, and combination of irinotecan and cisplatin to treat clear cell carcinoma are used as a first-line chemotherapy.

3. Second-line chemotherapy (salvage, consolidation, maintenance chemotherapy)

Aggressive surgical cytoreduction followed by six cycles of carboplatin plus paclitaxel represents the standard of care for ovarian cancer, from stage 1C to IV [8,9,12-14]. Despite the high response rate reported with this strategy, most (50 – 75%) of the patients who have a complete response relapse ultimately die of ovarian cancer [15,26].

Several types of consolidation treatments have been tested, such as radiotherapy [27,28], hormonal therapy [29] and immunotherapy [30,31]. Most of these studies had small sample size and insufficient power; all of them produced negative results. Recently, two studies have been reported on the use of systemic chemotherapy as consolidation treatment with paclitaxel and epirubicin [32,33]. Markman *et al.* [32] showed that 12 cycles of single-agent paclitaxel, compared with 3 cycles of the same drug, significantly prolonged progression-free survival in patients with clinical complete response to first-line carboplatin and paclitaxel. This study was discontinued early after an interim analysis showed a statistically significant improvement in time to progression, with a 7-month advantage for the arm receiving 12 cycles compared with that receiving 3 cycles. This is the first randomised study that has suggested that maintenance chemotherapy may impact survival. In addition, it has been reported that chronic administration of single weekly paclitaxel in heavily pretreated ovarian cancer patients could be safely used and resulted in long progression-free interval [34].

Another trial with negative results has been reported in abstract form by Scarfone *et al.* [33], comparing four cycles of epirubicin (120 mg/m^2) with no treatment in the same setting of patients. Preliminary results (presented at the 2002 Annual Meeting of the American Society of Clinical Oncology) indicate that there was no advantage in time to progression for patients treated with epirubicin. The addition of epirubicine to the standard carboplatin and paclitaxel treatment did not improve progression-free survival [35,36].

Improvements in ovarian cancer management mean that it may now be a long-term disease for which treatment must be carefully considered. Optimal sequencing of chemotherapy may help to enhance patient's benefit of therapy and minimise toxicity. The response to retreatment with platinum or a platinum/taxane combination is strongly influenced by the treatment-free interval after initial therapy with a platinum combination. Response rates to platinum retreatment in platinum-resistant patients (relapse within 6 months) are lower than those in platinum-sensitive patients (relapse after 6 months). It is possible that if one was able to extend the interval until relapse, response rate to platinum may be improved. Therefore, increasing the platinum-free interval by using non-platinum-based chemotherapy for treatment after relapse appears to increase the response to later rechallenge with platinum [37]. Many alternative agents have been investigated for the treatment of patients with relapsed ovarian cancer. For the selection of the optimal chemotherapy regimen at first relapse, patients are usually characterised according to their degree of sensitivity or resistance to the treatment, depending on the interval between initial response and first relapse (< 3 months: refractory; < 6 months: resistance; 6 – 12 months: sensitive; 12 – 24 months: very sensitive) [37]. In addition to treatment-free interval, prediction of response includes a number of prior regimens, toxicity from prior therapy, previous use of growth factors and/or transfusions, performance status, volume of disease, number of disease site, ascites, and signs and symptoms of gastrointestinal dysfunction. At present, complete responses to treatment for recurrent disease are rare, particularly if the patient's time to relapse is short. Treatment-free intervals decrease after each relapse and retreatment, which may increase toxicities. The median survival after disease recurrence is in the range of 12 – 24 months [36]. As a general rule, the later the recurrence, the better the prognosis for survival duration. The aims of palliative treatment in relapsed ovarian cancer are, therefore, to control disease-related symptoms and minimise the side effects of treatment in order to prolong survival and delay time to progression. Maintenance or, preferably, improvement in quality of life becomes an important goal in these patients. A number of different strategies may be employed in the management of patients with relapsed ovarian cancer, including retreatment with platinum or salvage therapy with a variety of other agents, either alone or in combination regimens.

One treatment management option in relapsed patients is to reuse a platinum/taxane combination. However, response rates to such therapy are particularly low in patients with a short treatment-free interval. The correlation between platinum-free interval and response to second-line platinum

Table 1. Comparison of survival between adjuvant chemotherapy after initial debulking surgery and neoadjuvant chemotherapy followed by interval surgery.

	Comparison of survival	Comparison of debulking
Jacob (1991) [68]	Median survival	Optimal (%)
Adjuvant	18 months	39%
NAC therapy	16 months	77% (p = 0.02)
Onnis (1996) [70]	3- and 5-year	Optimal (%)
Adjuvant	survival	29%
NAC therapy	31 versus 21%	42%
	27 versus 19%	
Schwartz (1999) [71]	Median survival	
Adjuvant	2.18 years	
NAC therapy	1.07 years	
Vergote (1998) [72]	3-year survival	
Adjuvant	26%	
NAC therapy	42% (p = 0.001)	

NAC: Neoadjuvant chemotherapy.

combination therapy has been clearly demonstrated in number of studies [37-39]. The number of responders in the 6- to 12-months category is thought to be in the 25 – 30% range, slowly increasing to a rate of 60 – 70% at 2 years. Combinations of carboplatin and paclitaxel appear to have a higher response rate and may also blunt the platinum-free interval effect seen with single-agent platinum treatment [40]. This was also the result of the recently presented International Collaborative Ovarian Neoplasm 4 report [41]. The platinum-free interval has been used to classify relapsed patients for therapy. Essentially all agents appear to be more active in patients off therapy for > 6 months. Because all of these patients are currently incurable, the overall goal of therapy is to extend survival through a series of chronic treatments. The most beneficial sequence of treatments for particular patients has not been established.

A considerable number of nonplatinum agents have been investigated for the treatment of patients with relapsed ovarian cancer. Examples of efficacy with single-agent therapy with paclitaxel, topotecan (because topotecan is not approved in Japan, irinotecan is used), liposomal doxorubicin, etoposide and gemcitabine in recurrent ovarian cancer, as well as their known cumulative toxicities, have been shown [39-41,44-56].

Paclitaxel, a unique antimicrotubule agent, has been one of the most promising drugs to enter into clinical trials in the setting of cisplatin-refractory ovarian cancer. Responses have been reported in both heavily and minimally pretreated ovarian cancer patients (20 – 37%) [57]. However, myelotoxicity was found to be a major concern even with granulocyte colony-stimulating factor support. In order to minimise toxicity, paclitaxel can be given weekly instead of every 3 weeks [58,59]; this results in a higher dose intensity of the drug [58]. Two non-randomised trials [61,62] have suggested that the activity of paclitaxel in epithelial ovarian cancer is dose-dependent, and a randomised trial [58] has shown reduced toxicity with weekly scheduling without detriment to efficacy. It has been reported that single weekly paclitaxel has moderate activity in heavily pretreated ovarian cancer patients, and 80 mg/m^2 of paclitaxel was recommended as the Phase II dose for out-patients [63]. With 80 mg/m^2 of paclitaxel, the dose intensity may not be greater than once every three weeks. However, continuous low-dose paclitaxel has been reported to result in antiangiogenic effects and tumour dormancy [64,65]. Thus, the effects of single weekly paclitaxel in heavily pretreated patients with recurrent or persistent ovarian cancer were investigated. Thirty-seven patients were included in this intent-to-treat study. The overall clinical response rate was 45.9% (5 complete responses, 12 partial responses). The clinical response rate in patients with measurable tumour was 25.0% (2 complete responses, 1 partial response), whereas that in patients without measurable tumour and with assessable cancer antigen 125 (CA125) levels was 56.0% (3 complete responses, 11 partial responses). The criteria for response was based on declining CA125 levels as described by Rustin *et al.* [66]. Clinical response rates in patients with chemotherapy-free interval of > 6 months were around twice those found in patients with chemotherapy-free interval of < 6 months. The clinical response rate by number of prior regimens revealed that as number of prior regimens increases, the response rate decreases. Weekly paclitaxel has significant antitumour activity in heavily pretreated patients with recurrent or persistent ovarian carcinoma, and may be used as second- or third-line chemotherapy in such a setting [34]. Likewise, weekly administration of docetaxel has demonstrated comparable efficacy together with reduced myelosuppression in patients with solid tumours, including breast tumour, but not ovarian cancer [67].

4. Neoadjuvant chemotherapy

The clinical basis of aggressive cytoreductive surgery in the initial management of ovarian cancer is the significantly improved survival accrued to those patients in whom optimal cytoreductive surgery was accomplished [68,69]. The theoretical basis for primary cytoreductive surgery is supported by tumour cell growth kinetics observations that: an increase in cell-doubling time occurs as cancer becomes larger; resection of large tumour masses increases the number of residual cells that are in an active growth phase and are more sensitive to chemotherapy; and surgical cytoreduction results in an exponential reduction of tumour volume, thus leaving fewer cells to be eradicated [70]. These observations would suggest that neoadjuvant chemotherapy should, if anything, impair survival of women with advanced ovarian cancer. Some retrospective studies failed to demonstrate this as is shown in **Table 1**.

Although the prognosis for patients with advanced ovarian cancer has been improving over the last decades, long-term survival figures are still disappointingly low. More adequate therapeutic approaches need to be developed, especially for

patients whose tumours cannot be optimally debulked upfront. One such approach is the concept of chemical cytoreduction before debulking surgery in selected patients. Based on the available data, neoadjuvant chemotherapy in advanced ovarian cancer seems to allow for higher optimal debulking rates without compromising survival, and might be a valid alternative to upfront debulking surgery in patients with a high total metastatic load, stage IV disease, the presence of uncountable peritoneal metastases, or a poor performance status [71,72]. Some studies suggest that additional benefits may be reduced perioperative morbidity and increased quality of life. Hence, even if neoadjuvant chemotherapy followed by debulking surgery does not result in a better but similar overall survival compared with conventional treatment, it still may be a worthwhile approach based on considerations of morbidity, economic cost and quality of life. Some patients with primarily chemoresistant disease might also be spared the burden of an unnecessary laparotomy. All these issues have undoubtedly to be tested in a prospective randomised fashion. Until the results of such evaluations are available, neoadjuvant chemotherapy should not be considered as part of standard therapy in patients with advanced ovarian cancer, for whom the standard of care is still upfront maximal debulking surgery by an appropriately trained and experienced gynaecological oncologist.

5. Metronomic chemotherapy

Chemotherapeutic drugs, which have long been the mainstay of cancer treatment, cause DNA damage and disrupt DNA replication in proliferating cells. Drug regimens have been designated to kill as many tumour cells as possible by treating with MTDs of these cytotoxic agents. Side effects such as neurotoxicity and damage to proliferating cells in healthy tissues pose serious constraints on the use of chemotherapy. In an effort to balance toxicity with efficacy, a conventional dosing schedule calls for episodic application of a cytotoxicity drugs at or near the MTD, followed by periods of rest to allow normal tissues to recover. Many such chemotherapy regimens are initially efficacious, resulting in tumour regression or stabilisation and prolonged survival. In general, however, responses are short-lived, with relapses often marked by aggressive cancer that is resistant to the cytotoxic drug. Furthermore, the standard MTD regimen as a rule seriously impairs quality of life.

Although the collateral damage inflicted on the dividing bone marrow progenitors, gut mucosal or hair follicle cells by DNA damaging of microtubule inhibiting agents is certainly undesirable, the same cannot always be said of the damage inflicted on endothelial cells present in a tumour's growing neovasculature. A proportion of these cells are dividing at any given time, making them, at least in theory, sensitive to drugs that preferentially damage or destroy cycling cells [73]. Polverini's group first reported antiangiogenic effects mediated by conventional cytotoxic anticancer drugs as long ago as 15 years, and since then most common anticancer chemotherapeutic agents, belonging to all major classes, have been shown to be capable of inhibiting angiogenesis [74]. This prompted Sledge and colleagues [64] recently to suggest the notion of 'redefining' chemotherapeutic drugs as antiangiogenics. It is intriguing and perhaps reassuring to note that there are many clinical precedents for the observations of Browder *et al.*, as summarised recently by Kamen *et al.* [75], and by Gately and Kerbel [76]. For example, significant proportions of breast and ovarian cancer patients (≤ 62.5%) who had stopped responding to MTDs of a taxane given once every 3 weeks, were subsequently found to respond to the same drug once it was switched to a weekly schedule at about a third of the MTD [58,77-79]. Such weekly schedules using lower drug doses were instituted to minimise the toxicities associated with once-every-3-weeks MTD taxane protocols. It is not yet known whether the rsesponses observed in these 'resistant' patients have an antiangiogenic basis, or whether such increased response rates will translate into a significant prolongation of survival, as they do in mice [80,81].

Introduction of paclitaxel into the armamentarium of drugs to treat platinum-resistant ovarian cancer has been one of the more significant advances in the treatment of ovarian cancer in the last decade. Paclitaxel has a unique mechanism of action, is cell-cycle-specific, and acts by promoting the stability of the microtubule assembly during mitosis. *In vitro* data suggest that the duration of exposure plays a crucial role in the cytotoxicity efficacy of paclitaxel [82,83]. Resistance to paclitaxel-mediated P-glycoprotein [84] has been shown to be significantly reduced by increasing the duration of exposure to paclitaxel from 3 to 96 h in P-glycoprotein-expressing paclitaxel-resistant breast cancer cell lines [85]. Weekly administration of paclitaxel has the potential to have an effect similar to that of continuous infusion while taking advantage of the minimal haematological toxicity associated with shorter infusions [34]. Neutropenia was the most frequent haematological adverse event observed in patients receiving once-weekly intravenous paclitaxel monotherapy. Severe neutropenia was dose-related, occurring only in 3 – 15% of patients receiving 80 mg/m^2 monotherapy [86,87]. An absolute neutropenia count of 1000 has been shown to be sufficient for dosing weekly paclitaxel on any given scheduled day of treatment. In this study, severe neutropenia and leukopenia of grade 4 were observed in 2 (5.4%) and 1 (2.7%) of 37 patients, respectively. Other haematological adverse events such as grade 4 anaemia and/or grade 4 thrombocytopenia were not observed. Neuropathy is experienced by most patients receiving once-weekly intravenous paclitaxel monotherapy and is usually mild or moderate [86,87]. Treatment with single weekly 80 mg/m^2 paclitaxel brought about an overall response rate of 45.9%, which is similar to that of a recent report [88]. It is noteworthy that 5 complete responses among 37 patients with one or more therapeutic regimens were achieved.

The choice of second-line drug in this present setting is dependent on toxicity and quality of life considerations, in

Table 2. HER-2/neu and EGFR overexpression rate according to histological type.

Histology	HER-2/neu overexpression	EGFR overexpression
Serous	8/60 (13%)	24/60 (40%)
Endometrioid	0/15 (0%)	4/15 (27%)
Mucinous	2/11 (18%)	2/11 (18%)
Clear	6/26 (23%)	11/26 (42%)
Total	16/112 (15%)	41/112 (36%)

EGFR: Epidermal growth factor receptor; HER-2: Human epidermal growth factor receptor 2.

addition to efficacy. Weekly administration of paclitaxel by 1-h infusion has been reported to have less toxicity than other schedules and primary effect in patients with pretreated gynaecologic cancers [58,60,89,90]. In addition, a randomised Cancer and Leukemia Group B trial comparing the weekly schedules to paclitaxel given once every 3 weeks for advanced breast cancer is nearing completion. 'Metronomic' dosing or antiangiogenic scheduling of cancer chemotherapeutics has been increasingly recognised to be a potential application of paclitaxel in cancer therapy [91-93].

6. Molecular-targeted chemotherapy

Traditional cytotoxic agents cannot distinguish malignant from nonmalignant cells. As a result, use of these agents at clinically effective doses is often accompanied by severe toxicity. This lack of specificity has stimulated the development of a new breed of agents that primarily target growth and signalling processes in malignant cells and, thus, tend to be less toxic to normal cells than conventional cytotoxic therapies [94]. These specially engineered compounds largely target cell-membrane receptors that control the intracellular signal transduction pathways regulating cell proliferation and apoptosis, angiogenesis, cellular adhesion and cell motility.

6.1 Epidermal growth factor receptor inhibitors

The epidermal growth factor receptor (EGFR) is highly expressed in a variety of solid tumours, including ovarian cancer. Activation of the EGFR signalling pathways has been linked with increased cell proliferation, angiogenesis, metastasis and decreased apoptosis [95]. Preclinical studies have shown that blocking this pathway inhibits these processes both *in vitro* and *in vivo* and increases apoptosis of malignant cells, while having minimal effects on normal cell function. The authors' clinical studies revealed that overexpression of EGFR was observed in 36% of ovarian cancer and seemed to be greater in serous cystadenocarcinoma and clear cell carcinoma than in endometrioid adenocarcinoma and mucinous cystadenocarcinoma, although not significant (Table 2).

The anti-EGFR therapies currently undergoing clinical development are the monoclonal antibodies trastuzumab (Herceptin®, Genentech, Inc.) and cetuximab and small-molecule EGFR tyrosine kinase inhibitors gefitinib and erotinib (OSI-774/Tarceva™, OSI Pharmaceuticals, Inc.). Proliferation of ovarian epithelial cancer cells expressing HER-2/neu is blocked by trastuzumab *in vitro* [96], and the results of clinical testing at Ohio State University in ovarian cancer patients were shown to be inactive because of a small percentage of HER-2/neu-overexpressing tumours. In an immunohistochemical study, rate of HER-2/neu overexpression in ovarian cancer was 15%, and it is noteworthy that overexpression of HER-2/neu in endometrioid carcinoma was not observed, whereas clear cell carcinoma showed a higher staining rate (Table 2). A Phase I study of its safety in patients with a variety of tumours, including ovarian cancer, established that the drug was well-tolerated at doses of ≤ 600 mg/day and that treatment inhibited the EGFR signalling pathway [97].

Objective antitumour responses and evidence of disease stabilisation were documented in 34 patients with advanced platinum- and/or paclitaxel-resistant ovarian cancer who had been treated with erotinib [98].

6.2 Signal transduction inhibitors

Aberrant signal transduction has been implicated in malignant transformation, growth and progression. This has led to the proposal to use inhibitors of signal transduction pathways to treat cancer. Chronic myelogenous leukaemia (CML), for example, is characterised by a translocation between chromosomes 9 and 22. The fusion of the *Abl* gene on chromosome 9 with the *Bcr* gene on chromosome 22 forms a *Bcr-Abl* fusion gene that expresses tyrosine kinase, which is thought to be leukaemogenic. Imatinib mesylate (STI-571/Gleevec®, Novartis Pharmaceuticals Corporation) is a potent inhibitor of *Bcr-Abl* tyrosine kinase and selectively kills *Bcr-Abl*-expressing tumour cells. Recent studies have shown that several tumours express c-KIT: a growth factor receptor with tyrosine kinase activity; moreover, clinical results have shown the efficacy of the tyrosine kinase inhibitor, imatinib mesylate, in c-KIT-positive tumours. Intense c-KIT immunostaining was observed in 51.7% of cases. c-KIT expression was statistically correlated with progression of disease after first-line chemotherapy. c-KIT is also expressed in ovarian carcinoma and it is statistically correlated with chemotherapy resistance. Clinical trials confirming the utility of the tyrosine kinase inhibitor, imatinib mesylate, in advanced ovarian cancer patients with c-KIT overexpression who have shown no clinical response to conventional chemotherapy are warranted [99]. Clinical trials of imatinib mesylate in ovarian cancer are being conducted by the Gynecologic Oncology Group (GOG), National Cancer Institute and the Southwest Oncology Group. The PI3K/AKT pathway stimulates cell proliferation, inhibits apoptosis and increases drug resistance. The upregulation of the P110-α catalytic subunit of PI3K is often found in human ovarian cancer [100]. Kudoh *et al.* (pers. commun.) observed marked sensitising effect of PI3K inhibitor LY-294002 (Calbiochem) on antitumour effect of paclitaxel in a

paclitaxel-resistant human ovarian cancer cell line. The synergistic augmentation of the cytotoxocity by PI3K inhibitor LY-294002 occurs specifically with antimicrotubule agents, at least partially through an increase in caspase 3-dependent apoptosis, so that inhibitors of the PI3K/AKT pathway in combination with antimicrotubule agents may induce cell death effectively and be a potent modality to treat patients with malignant tumours [101]. PI3K inhibitor is a promising therapy strategy in drug-resistant ovarian cancer [102].

6.3 Antiangiogenesis therapy

Angiogenesis, the formation of new blood vessels, is essential to the growth and proliferation of solid tumours. Presumably, anything that interferes with angiogenesis will cause the tumour to 'starve' and eventually kill it, a concept originally proposed by Folkman [103]. Tumour angiogenesis may be regulated by angiogenic factors such as VEGF [104] and IL-8 [105]. Of the known proangiogenic factors, VEGF is one of the most potent and specific, and it has been identified as a crucial regulator of both normal and pathological angiogenesis. Overexpression of VEGF has been demonstrated in most human cancers, including ovarian tumours. Bevacizumab is a recombinant anti-VEGF monoclonal antibody that recognises all biologically active isoforms of VEGF and blocks their binding to VEGF receptors, thus inhibiting angiogenesis [104]. A Phase II clinical trial, designed and implemented by the GOG protocol 170D, is currently underway to access the safety and efficacy of bevacizumab in patients with recurrent or persistent ovarian cancer. Also being investigated as a potential antiangiogenesis agent in ovarian cancer is thalidomide, which is showing some benefit in women refractory to conventional chemotherapy [106], and RPI-4610 (Angiozyme, Sirna Therapeutics, Inc.), a proprietary ribozyme that can downregulate VEGF receptor function by specifically cleaving the mRNA for a primary VEGF receptor: FLT-1. Clinical trials are currently in progress to establish the therapeutic efficacy and safety of RPI-4610 in patients with advanced malignancies. Extensive preclinical studies have demonstrated no significant toxicities [107]. Another antiangiogenic molecule under development is the PKC-β inhibitor LY-317615. This small, orally available molecule has demonstrated the ability to inhibit growth-factor-driven proliferation of tumour neovascularisation and is currently undergoing Phase I testing in several tumour types [108]. Recently, it has been reported that bisphosphonates (pamidronate) induce significant and lasting modifications of angiogenic cytokine patterns [109]. Experimental trials should be addressed to assess the real clinical impact in anticancer therapy of antiangiogenic properties of bisphosphonates.

The inducible enzyme cyclooxygenase-2 (COX-2) is an important mediator of angiogenesis and tumour growth. Selective COX-2 inhibitor drugs, commonly prescribed for pain management, are now being evaluated for their antitumour and antiangiogenic activities. These drugs include celecoxib (Celebrex®, Pfizer, Inc.), rofecoxib (Vioxx®, Merck & Co, Inc.) and valdecoxib (Bextra®, Pfizer, Inc.). Oral celecoxib (30 mg/kg/day) inhibited angiogenesis by 79% in a rat model of basic fibroblast growth factor (bFGF)-induced cornel angiogenesis, and reduced corneal levels of prostaglandin E2 and thromboxane 2 by 79 and 68%, respectively [110]. Celecoxib can also inhibit angiogenesis via COX-2-independent mechanisms. Impaired VEGF gene expression and decreased angiogenesis result from celecoxib-induced interference with DNA binding of the Sp1 transcription factor [111]. Celecoxib has also been reported to increase serum levels of the endogenous angiogenesis inhibitor endostatin, while decreasing the release of VEGF by platelets [112], thus altering the balance of angiogenesis regulation in favour of inhibition. A Phase II study of lung cancer patients receiving celecoxib 400 mg b.i.d. p.o. concurrently with paclitaxel/carboplatin plus radiation therapy found that serum/plasma levels of VEGF declined at 2, 5 and 7 months following treatment [113]. Rofecoxib also has been shown to inhibit angiogenesis in a number of *in vivo* systems. Administration of rofecoxib blocks the production of bFGF and reduces wound healing angiogenesis in experimental gastric ulcers [114]. In a model of retinopathy, rofecoxib inhibited neovascularisation in COX-2-expressing retinal vessels [115]. Based on supportive preclinical data, a large-scale clinical trial is underway in Europe studying rofecoxib as an adjuvant antiangiogenic treatment in 3500 patients with previously resected colorectal cancer. Although no clinical trials in ovarian cancer have been carried out, trials in such an adjuvant setting are awaited.

7. Conclusion

The management of ovarian cancer begins with appropriate surgical staging. Following surgical staging and removal of the reproductive organs, adjuvant chemotherapy has been performed. The standard regimen over the past several years has been a combination of carboplatin (area under the curve: 5 – 7.5) plus paclitaxel (175 mg/m^2, infused over 3 h). Studies carried out by GOG, as well as several European trials, have demonstrated optimum response rates with this combination, and it has come to be accepted as the 'gold standard' for treating ovarian cancer. Although this regimen has resulted in prolongation of survival times, only modest improvement of overall survival has been observed with this treatment strategy.

Recurrent ovarian cancer patients with platinum-refractory disease can still respond to platinum retreatment following treatment with continuous low-dose paclitaxel. In patients with platinum-resistant disease the use of intervening therapy to extend the platinum-free interval may be a useful strategy, providing a similar immediate response rate and an improved response to platinum later.

At present, solid evidence demonstrating the superiority of neoadjuvant chemotherapy followed by postdebulking chemotherapy over conventional postdebulking chemotherapy alone is lacking, but further study is needed. Elderly and medically

compromised patients with massive ascites are excellent candidates for neoadjuvant chemotherapy, as it avoids postoperative fluid shifts, which can stress the cardiovascular integrity of these patients.

Some patients who are receiving long-term maintenance or even palliative chemotherapy continue to have stable disease beyond the time that the tumour cells would have been expected to develop drug resistance. A closer approximation to antiangiogenic scheduling may explain the improved outcome of empiric treatment of 'slower growing' human cancer using continuous infusion 5-fluorouracil in breast cancer and colorectal cancer [116-118], weekly paclitaxel in recurrent ovarian cancer and pretreated solid tumours [119,120], and daily oral etoposide in non-small cell lung cancer and in supratentorial malignant glioma in children [121-123]. If this hypothesis proves generalisable, it may suggest which agents and on which schedules chemotherapy may be best combined with more specific angiogenesis inhibitors for improved antiangiogenic and anticancer efficacy.

Molecular-targeted therapy could be considered, using novel agents capable of homing in on a single molecular target that is overexpressed in cancer cells, but lacking in normal cells. These gene- and target-based therapies are able to become new treatment strategies with less toxicity than conventional treatment modalities. The application of these new treatment strategies to ovarian cancer is still in its infancy. Recently, it has been reported that in a stringent preclinical model, standard chemotherapy followed by a novel maintenance regimen resulted in disruption of pericyte support by plasmid-derived growth factor receptor and subsequent metronomic chemotherapy and/or VEGF receptor inhibitors target consequently sensitised endothelial cells, collectively destabilising pre-existing tumour vasculature and inhibiting ongoing angiogenesis [124]. This exciting translational work requires many disciplines and organisations to work together internationally to accelerate patient benefit.

8. Expert opinion

Poor prognosis of ovarian cancer compared with uterine cervical cancer and endometrial cancer is due to incapability of early diagnosis. Ovarian cancer presents at a late clinical stage in > 75% of patients, and is associated with a 5-year survival of 35% in this population. By contrast, the 5-year survival for patients with Stage I ovarian cancer is > 90%, and most patients are cured of their disease by surgery alone. Therefore, increasing the number of women diagnosed with Stage I disease should have a direct effect on the mortality and economics of this cancer without the need to change surgical or chemotherapeutic approaches. A global view of the proteome would enhance the possibility of identifying protein signatures for ovarian cancer. Surface-enhanced laser desorption and ionisation with time of flight detection (SELDI-TOF) spectral analysis was linked with a high-order analytical approach using samples from women with a known diagnosis to define an optimum discriminatory proteomic pattern. This pattern was used to predict the identity of masked samples from unaffected women, women with early and late-stage ovarian cancer, and women with benign disorders. Following proper validation, serum proteomic pattern analysis might be ultimately applied in medical screening clinics, as a supplement to the diagnostic workup and evaluation. A negative value, if the sensitivity remains at 100% on further trials, could be used for reassurance, whereas a positive value may be sufficient to warrant further evaluation. An important future goal is confirmation of sensitivity and specificity for the prospective detection of Stage I ovarian cancer in trials of high- and low-risk women, respectively. It will be important to design the trial to evaluate the efficacy of the approach as a standalone approach or one to be combined with current screening options. Such trials should benefit patients, particularly ovarian cancer patients.

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