Additional Statements:

Cisplatinum agent:

(1) A randomized, controlled study examined groups that received cyclophosphamide 600mg/m^2 + carboplatin 300mg/m^2 + doxorubicin 50mg/m^2 or ifosfamide 5g/m^2. One group received the combination every 4 weeks for six cycles and the other group received half the amount every 4 weeks for 12 cycles. The clinical efficacy rate was significantly higher in the dose-intensive chemotherapy group.[18)]

(2) A randomized, controlled study compared the administration of two doses of cisplatin (50 or 100 mg/m^2) plus cyclophosphamide 750 mg/m^2 for six cycles. The patient group receiving 100 mg/m^2 cisplatin in combination with cyclophosphamide showed a significantly higher efficacy rate than the group 50 mg/m^2 cisplatin.[19)] However, a subsequent study[20)] showed that there was no significant difference between the two groups with regard to their long-term prognosis. Therefore, the recommended cisplatin dose was stated to be 75 mg/m^2 every 3 weeks.

(3) Although there have been randomized, controlled studies since 1995[21)~25)] using 'dosed-up' platinum agents, there are no reports of significant differences in the results of the different treatment regimens. Thigpen[26)] indicated that there is an increasing therapeutic effect of cisplatin with increasing doses up to 25 mg/m^2 per week, but the effects may plateau with doses higher than this.

Table 7 Comparison of the Toxicity and Other Factors of Cisplatin and Carboplatin

	Cisplatin	Carboplatin
Thrombocytopenia	<	
Neurotoxicity	>	
Nephrotoxicity	>	
Digestive symptoms	>	
Convenience of pretreatment	<	
Compliance	<	
Antitumor effect	≒	

Meta-analysis (ovarian cancer cases $n = 5667$).

Table 8 Comparison of Paclitaxel Toxicity as a Function of Time

	Infusion time	
	24h	3h
Hypersensitivity reaction		≒
Neutropenia		>
Neurotoxicity		<

Table 9 Paclitaxel + Cisplatin (TP Therapy) Versus Paclitaxel + Carboplatin (TJ Therapy)

Author (study)	Cases	Chemotherapeutic agents	Results
Bois[7)8)] (AGO)	Stage II–IV, 798 cases	Paclitaxel 185mg/m^2 over 3h, cisplatin 75mg/m^2	PFS: 19.1months OS: 44.1months
		Paclitaxel 185mg/m^2 over 3h, carboplatin (AUC = 6)	PFS: 17.2months OS: 33.3months
		Paclitaxel 135mg/m^2 over 24h, cisplatin 75mg/m^2	PFS: 19.4months OS: 48.7months
Ozols[6)] (GOG158)	Stage III, 840 cases optimal	Paclitaxel 175mg/m^2 over 3h carboplatin (AUC = 7.5)	PFS: 20.7months OS: 57.4months

In both studies, there was no difference in survival rate, but toxicity was higher for TP therapy.
PFS, progression-free survival; OS, overall survival.

C. Options for Standard Remission-Induction Therapy and Adjuvant Chemotherapy [II/III, B]

Docetaxel + carboplatin (DJ therapy)	• Docetaxel: 60–75 mg/m^2 • Carboplatin: AUC = 5–6 i.v., day 1, every 3-4 weeks, total 6 cycles
Cyclophosphamide + doxorubicin + cisplatin (CAP therapy)	• Cyclophosphamide: 500 mg/m^2 • Doxorubicin: 30–50 mg/m^2 (Terarubicin: 30 mg/m^2, epirubicin 50 mg/m^2) • Cisplatin: 50–75 mg/m^2 i.v., Day 1, every 3–4 weeks, total six cycles
Cyclophosphamide + cisplatin (CP therapy)	• Cyclophosphamide: 800–900 mg/m^2 • Cisplatin: 60–75 mg/m^2 i.v., Day 1, every 3–4 weeks, total six cycles
Paclitaxel + carboplatin weekly administration (weekly TJ therapy)	• Paclitaxel: 60–80 mg/m^2, Days 1, 8, 15 • Carboplatin: AUC = 6, day 1, Or AUC = 2, Days 1, 8, 15
Cyclophosphamide + carboplatin (CJ therapy)	• Cyclophosphamide: 800–900 mg/m^2 • Carboplatin: AUC = 5–6 i.v., Day 1, every 3–4 weeks, total six cycles
Cisplatin or carboplatin monotherapy	• Cisplatin: 75–100 mg/m^2 Or • Carboplatin: AUC = 5–6 i.v., Day 1, every 3–4 weeks, total six cycles
Cisplatin + carboplatin concomitant therapy (JP therapy)	• Carboplatin: AUC = 5–6, Day 1 • Cisplatin: 60–75 mg/m^2, Day 3 i.v., every 3–4 weeks, total six cycles
Irinotecan + cisplatin	• Irinotecan: 60 mg/m^2, Days 1, 8, 15 • Cisplatin: 60 mg/m^2, Day 1 i.v., every 4 weeks, total six cycles

Remarks

1. No results have been reported yet concerning the contribution of docetaxel and carboplatin (DJ therapy) on long-term survival; therefore, this therapy cannot be assessed at this time. That is, it is premature to consider this particular treatment as a standard initial-stage therapy for ovarian cancer. However, DJ therapy may be the treatment of choice for those patients in whom the complication of peripheral neuropathy is a concern.

SCOTROC Study[1] Protocol:
DJ therapy: Docetaxel (75 mg/m^2 1-h infusion) + carboplatin (AUC = 5) compared with
TJ therapy: Paclitaxel (175 mg/m^2 3-h infusion) + carboplatin (AUC = 5)
Every 3 weeks, total six times
Study design: Randomized, controlled study
Subjects: 1077 cases
Results (DJ *vs.* TJ):
Efficacy rate: 65% *vs.* 62%, indicating equal efficacy
PFS: 15.1 *vs.* 15.4 months, no difference
2-year survival rate: 65.5% *vs.* 69.8%, no difference
The occurrence of myalgia was low in DJ therapy
Neurotoxicity: 11% *vs.* 30%
Myelosuppression: 92% *vs.* 84%, no improvement in hypersensitivity reaction
Point in question: Unknown long-term prognosis

2. In addition to the standard TJ therapy and DJ therapy, other treatment selections, depending on individual cases, are:
   - weekly TJ therapy;[2]
   - conventional CAP therapy and CP therapy;
   - platinum monotherapy[3,4] or concomitant (JP) therapy;[5,6]
   - taxane monotherapy
   - irinotecan + cisplatin therapy.[7]

Additional Statements:

Weekly concomitant administration of paclitaxel and carboplatin is being noted for the following reasons.

(1) TJ weekly therapy:
   a. Significantly lower myelosuppression compared with standard administration.
   b. No significant differences in other adverse side-effects have been observed.
   c. No significant difference in efficacy rate compared with standard administration.
   The doses used are paclitaxel 60 mg/m^2 and carboplatin AUC = 2.[2]
   However, there is no basis for selecting different schedules of carboplatin administration (one-time administration or in weekly divided doses).

(2) Double platinum (JP) therapy:
   Concomitant therapy of carboplatin and cisplatin (every 4 weeks) is also recognized as a treatment for advanced ovarian cancer. However, there is the adverse side-effect of auditory dysfunction in addition to a relatively high degree of myelosuppression.[5] In Japan, the dosing schedule based on a phase I clinical study is carboplatin AUC = 5–6, Day 1 + cisplatin 60–70 mg/m^2, Day 2.[6]

D. Points to Consider at the Time of Chemotherapy

1. The sequence of administration of chemotherapeutic agents for TJ therapy is paclitaxel→carboplatin **[III, A']**.

Remarks

The clearance of paclitaxel administered after cisplatin decreases 25%. For this reason, myelosuppression is higher than that resulting from paclitaxel alone; however, by administering cisplatin after paclitaxel, the decreased clearance of paclitaxel and increased myelosuppression can be avoided.[1] Therefore, the general method is to administer cisplatin or carboplatin after the administration of paclitaxel.

2. The dose of carboplatin to be administered is calculated as AUC and not mg/m^2 **[III, A']**.

Remarks

Accurate calculations of the carboplatin AUC schedule should be made based on ^{51}Cr EDTA clearance.[2] However, in many cases for routine treatment with carboplatin, the AUC is calculated using a simplified method of glomerular filtration rate (GFR) calculation based on the reports of Cockroft[3] and Jellife:[4]

Carboplatin dose by Calvert = target AUC × (GFR + 25)

GFR = (98–0.8 × (age–20))/serum creatinine × body surface area/1.73 × 0.9 (according to Jelliffe[4])
GFR = ((140–age) × weight)/(72 × serum creatinine) × 0.85 (females) (according to Cockroft[3])
GFR = (98–0.8 × (age–20))/serum creatinine × 0.9 (according to GOG[5])

Additional Statements:

(1) The efficacy rate reaches its limit for an AUC over 7.[6]

(2) When carboplatin and other agents are used concomitantly, hemotoxicity and efficacy rate are correlated only with AUC.[7] No randomized, controlled study presently exists examining carboplatin administration in doses calculated as mg/m^2 compared with AUC. However, for the reason mentioned previously, calculation of the dose of carboplatin is recommended in AUC.

(3) The AUC value that is calculated by the above simplified method can underestimate the target AUC by 20%.[2]

(4) A calculation method to determine the optimal AUC of carboplatin to be used concomitantly with paclitaxel has not been established.

3. Owing to hypersensitivity reactions to palcitaxel and carboplatin (Table 10), premedication prior to TJ therapy is necessary **[III, A']**.

Table 10 Acute Hypersensitivity Reaction to Paclitaxel and Carboplatin

	Paclitaxel	Carboplatin
Frequency	Approximately 4%	Approximately 12%
Onset	Many cases after initial or second administration	After long-term treatment, the median being after the 8th administration (range 6–21); rare after initial or second or third administration, many cases (50%) show onset at a half-way point of therapy
Symptoms	Diffuse erythroderma, tachycardia chest tightness, dyspnea, hypertension, hypotension	Diffuse erythroderma, tachycardia, chest tightness, dyspnea, hypertension, hypotension
Readministration	Possible to readminister after steroid administration	Cannot readminister; readministration even after treatment, such as with steroid, causes symptoms to reappear
Pretreatment	• Dexamethasone 20mg, i.v.,12–14h and 6–7h prior to paclitaxel administration; ranithidine 50mg, i.v., and diphenhydramine 50mg, p.o., 30min prior to paclitaxel administration Or • Short-course premedication: dexamethasone 20mg, i.v., ranithidine 50mg, i.v., and diphenhydramine 50mg, p.o., 30min prior to paclitaxel administration	

Based on published data.[8)~10)]

E. Supportive Therapy

Supportive therapy is divided into two categories: (i) that provided in response to the adverse side-effects of chemotherapy; and (ii) therapy provided in response to the symptoms of ovarian cancer. When performing chemotherapy for ovarian cancer, if necessary, supportive therapy is provided.

1. Measures against myelosuppression.
   Routine use of colony stimulating factor (CSF) is not recommended. As a general rule, individual factors of each case must be considered before the use of CSF **[III, A']**. Granylocyte CSF (G-CSF) is to be used in accordance with the *Guidelines for G-CSF Usage* by the Japan Society of Clinical Oncology Clinical Study Committee 2001[1] **[III, A']**.

Remarks

In 2001, the Japan Society of Clinical Oncology presented new *Guidelines for G-CSF Usage*,[1] which were based on the CSF usage guidelines proposed by the American Society of Clinical Oncology (ASCO).[2)~4)] These guidelines were created using a high level of evidence on the basis of the results of clinical studies. When an individual reference is considered, the evidence level is I or II. However, because these guidelines are a collection of a considerably body of evidence, the evidence quality of the guidelines themselves was designated as level III. The strength of recommendation is level A' because of the statement that one must thoroughly familiarize oneself with and follow the guidelines.

Additional Statements:

The frequency of febrile neutropenia (FN) increases synergistically with increased doses of chemotherapeutic agents administered. During chemotherapy of recurrent cases, FN is more severe and occurs at a higher frequency than at initial treatment. The use of CSF agents is divided into the following categories: (i) therapeutic; (ii) primary preventative; and (iii) secondary preventative.

(1) Therapeutic administration.

a. During chemotherapy, the risks of FN and severe infectious disease are inversely related to the absolute neutrophil count.[5)]

b. If the absolute neutrophil count is less than 100/μL for 2 weeks, the risk of concurrent severe infectious disease increases significantly.[6)]

c. The results of multiple randomized, controlled studies (placebo *vs.* CSF) showed that CSF administration for FN shortened the length of hospitalization and allowed early improvement in the neutrophil count (> 500/μL). However, there have been no reproducible results in afebrile cases. Therefore, the CSF usage guidelines[2)~4)] proposed by the ASCO indicate that the preferred treatment for FN should be supportive therapy and antibiotic treatment. In addition, CSF use should be restricted to cases in which neutropenia continues for over 10 days and active complicated infections exist.[7)]

d. From the indications set by the [Japanese] insurance system, Japan recognizes cases with neutropenia caused by chemotherapy with neutrophil counts less than 1000/μL and febrile temperatures of more than 38°C continuing for 4–5 days, as well as cases with neutrophil counts less than 500/μL.

(2) Preventative administration.

As a general rule, administration for primary prevention is not recommended. Preventative administration is considered for cases in which the risk of severe neutropenia is over 40%.[7)]

Routine CSF administration for secondary prevention (CSF use at the second chemotherapy cycle) is not recommended. The duration of hospitalization, neutropenia, and antibiotic use is shortened by the administration of CSF, but there has been no improvement in survival time following CSF administration and chemotherapy.[7)~10)]

As criteria for CSF administration, the following conditions are given:

a. Pre-existing neutropenia;

b. Recurrent FN cases after previous chemotherapy with a different anticancer therapy;

c. Previous radiation therapy;

d. End-stage cancer;

e. Malnutrition;

f. Performance status 3 or 4; and

g. Existing infectious disease.

If FN occurred under conditions in addition to those mentioned above during previous chemotherapy, a reduction in the amount of chemotherapeutic agents should be first considered. Exceptions are cases involving, for example, germ cell tumors in which continuation of chemotherapy can lead to complete recovery.[7)]

2. Measures against digestive symptoms.
Because pain from digestive symptoms comprises a large part of the subjective symptoms, its relief is also one of the important aspects of supportive therapy[11] **[II, A]**.

Remarks

The degree of nausea caused by each type of anticancer agent and the recommended anti-emetic agents are given in Table 11.

Table 11 Degree of Nausea During Ovarian Cancer Chemotherapy with Particular Drugs and Anti-emetic Agents

Anticancer agents	Nausea		Pharmacotherapy
	Frequency	Level	
Cisplatin	90% or more	5	Dexamethasone, granisetron, ondansetron, azasetron, ramosetron
Carboplatin	60–90%	4	Dexamethasone, granisetron, ondansetron, azasetron, ramosetron, metoclopramide, tropisetron (p.o.)
Cyclophosphamide, doxorubicin, epirubicin, ifosfamide, irinotecan	30–60%	3	
Docetaxel, etoposide, paclitaxel	10–30%	2	Dexamethasone, prochlorperazine, metoclopramide, diphenhydramine
Bleomycin	10% or less	1	

From *Practice Guidelines in Oncology*, version 1 (2002, Ovarian Cancer Guideline, Jenkintown; revised from the 2001 publication).
NCCN, National Comprehensive Cancer Network.

F. Neoadjuvant Chemotherapy

By performing neoadjuvant chemotherapy (NAC), the tumor resection rate increases during IDS or SDS, the PFS time increases, and QOL improves. However, opinions are divided as to improvements in the long-term survival rate **[III, C]**.

Remarks

For advanced-stage ovarian cancer, remission-induction therapy has been performed after maximum debulking at initial surgery. In cases where complications exist or there is high surgical stress from procedures such as intestinal resection, PFS and QOL decrease, and the transition to chemotherapy may be delayed. In such cases, as well as in cases in which optimal debulking is determined to be difficult or impossible, the usefulness of NAC is being examined. Many reports from retrospective studies indicate that PFS and QOL improve by performing IDS or SDS after NAC, such as CAP therapy and CP therapy. However, there are only a few reports regarding the contribution of NAC to improvements in the overall survival rate.[1)~8)]

Additional Statements:

(1) With regards to the contribution of NAC in the improvement of PFS and OS, we await results of ongoing prospective, randomized, controlled studies, namely EORTC-5597[9)] using TP or TJ therapy as the NAC regimen and SWOG-S0009 using TJ therapy.

(2) The NCCN guidelines indicate chemotherapy (NAC) only after cytological diagnosis has been performed for clearly unresectable cases. The problems are diagnosis of the primary lesion, cytological diagnosis, and the determination of stage. The JCOG study is also investigating whether diagnostic laparotomy and laparoscopy are required.

G. Maintenance Chemotherapy (Maintenance and Consolidation)

1. There are no indications regarding the usefulness of maintenance chemotherapy for early stage ovarian cancer (stages I and II) **[II, C]**.
2. There have been occasional reports that have indicated the usefulness of maintenance chemotherapy (consolidation therapy) for cases of advanced cancer (stages III and IV). However, there have been no reports indicating an improvement in the long-term survival rate following maintenance chemotherapy **[II, B]**.

Remarks

There are high-risk cases in which a high frequency of recurrence exists even for an early stage cancer and, for such cases, maintenance chemotherapy may be performed. However, there is generally a low recurrence rate in cases of early stage cancer and there needs to be a large number of cases recorded in clinical studies to verify the usefulness of maintenance chemotherapy. For this reason, there have been many clinical studies performed using various regimens, but the results do not statistically indicate the usefulness of maintenance chemotherapy in cases of early stage cancer.[1)~3)]

Conversely, even if tumorectomy is performed, microscopic residual lesions inevitably remain in many cases of advanced ovarian cancer. There is a need to perform postoperative chemotherapy for the induction of remission. It has been reported that recurrences occurred in 20%–50% of cases with negative SLO and who were supposedly in clinical remission after remission-induction therapy. For this reason, a definite need for remission-induction chemotherapy (consolidation therapy) has been considered for cases of advanced-stage cancer that have been determined to be in remission.

Additional Statements:

(1) Limited maintenance chemotherapy for early stage cancer.

The GOG175 study[4)] is a clinical study for a high-risk early stage cancer that is currently in progress. Patients were randomly divided into groups to compare PFS and OS. After complete resection followed by three cycles of TJ therapy, one group is receiving weekly paclitaxel 40 mg/m^2 for 24 weeks, whereas another group is undergoing follow-up examinations only. The results of this study have not yet been reported.

(2) Maintenance chemotherapy (consolidation therapy) for advanced cancer (stages III and IV).

a. A collaborative clinical study between SWOG9701 and GOG178 has been undertaken.[5] Markman *et al.* examined consolidation therapy in subjects who achieved clinical CR of advanced ovarian cancer, fallopian tube cancer, and primary peritoneal cancer after five to six cycles of platinum–paclitaxel concomitant therapy. Subjects were divided randomly into two groups, one of which received consolidation therapy of paclitaxel every 4 weeks for three cycles and the other group received the consolidation therapy for 12 cycles. The median PFS of the former group was 21 months, whereas that of the latter group was 28 months ($P = 0.0023$). The group undergoing 12 cycles of consolidation therapy showed a significantly more favorable prognosis than the group undergoing three cycles of consolidation therapy. Based on these results, the SWOG Data/Safety Monitoring Committee encouraged termination in the middle of the study. However, it was decided that follow up of OS must continue; however, these results have not yet been reported.

b. There are other prospective, randomized, controlled studies that have shown statistically significant differences following the use of consolidation therapy. Barakat *et al.*[6] examined intraperitoneally administered cisplatin 100mg/m^2 and etoposide 200mg/m^2 every 4 weeks for three cycles. Cure[7] examined high-dose chemotherapy with carboplatin and cyclophosphamide using peripheral blood stem cell transplant (PBSCT). Both groups reported significant improvements in prognosis with their consolidation therapies.

c. There have been randomized, controlled studies that did not show any significant usefulness of consolidation therapy. Hakes *et al.*[8] reported on the use of CAP therapy (every 4 weeks for five *vs.* 10 cycles) and Bertelsen *et al.*[9] reported on the use of CAP therapy (every 4 weeks for six *vs.* 12 cycles). The completion rate was poor in both studies owing to the side-effects of the platinum agents, specifically neurotoxicity, nephrotoxicity, and nausea. In contrast, levels of neurotoxicity, nephrotoxicity, nausea, and myelosuppression are low for paclitaxel. Therefore, paclitaxel has been considered for long-term administration in consolidation therapy. Recently, the number of studies using paclitaxel has increased, such as the studies of Boruta *et al.*[10] and Markman *et al.*[5] Some of the studies that are presently in progress include AGO-GINECO OVAR[7], using four cycles of topotecan after six cycles of TJ therapy, and EORTC55875, using four cycles of intravenous cisplatin. The results of these studies have not yet been published.

Table 12 Maintenance Chemotherapy After Remission Using Remission-Induction Therapy (Consolidation Therapy)

Reference (study)	Year	Published regimen	Results
Chirara[11] (GONO)	1995	Platinum-based regimen *vs.* follow-up examinations	DFS
Barakat[6]	1998	Cisplatin 100mg/m^2, i.p. + etoposide 200mg/m^2, i.p. every 4 weeks, three cycles *vs.* follow-up examinations	DFS*
Boruta[10]	2002	Weekly administration of paclitaxel 80mg/m^2 *vs.* follow-up examinations	End result
Markman[5] (GOG178/SWOG9701)	2002	Paclitaxel 175mg/m^2 → 135mg/m^2, every 4 weeks, three *vs.* 12 cycles	DFS*

The results column lists the end-points that showed significant differences between the treatment groups.
*Significant differences in efficacy were observed when the patient groups were compared.
High-dose chemotherapy is another type of consolidation therapy.
DFS, disease free survival; OS, overall survival.

H. Intraperitoneal Chemotherapy

Presently, the intraperitoneal administration of anticancer agents has not replaced intravenous administration as a standard method **[I, C]**.

Remarks

In intraperitoneal chemotherapy (Ip therapy), high concentrations of the anticancer agent come in direct contact with the intraperitoneal lesions of ovarian cancer. This type of chemotherapy has been investigated using cisplatin as the main chemotherapeutic agent.[1] The results of a randomized, controlled study comparing intravenous and intraperitoneal administration were first reported in 1996.

Additional Statements:

(1) A SWOG, GOG, and ECOG collaborative clinical study has been reported.[2] The administration of cisplatin (i.v.) + cyclophosphamide (i.v.) and cisplatin (i.p.) + cyclophosphamide (i.v.) was examined in 654 cases of ovarian cancer stage III (residual tumor diameter < 2 cm). Compared with patients receiving conventional i.v. administration, the patient groups receiving i.p. cisplatin showed significantly more favorable results in terms of median survival rate (41 *vs.* 49 months, respectively) and mortality risk (1 *vs.* 0.76, respectively). Another advantage of i.p. therapy is the relatively fewer adverse reactions associated with it, including a significantly lower occurrence of auditory dysfunction and granulocytopenia.

(2) In the GOG, SWOG, and EGOG collaborative clinical study,[3] the administration of paclitaxel (i.v.) + cisplatin (i.v.) and carboplatin (i.v.) for two cycles + paclitaxel (i.v.) + cisplatin (i.p.) was examined in 462 cases of ovarian cancer stage III (residual tumor diameter < 1 cm). A significant lengthening of PFS was observed in the i.p. group compared with the other patient group (28 *vs.* 22 months, respectively), as well as an increase in OS (63 *vs.* 52 months, respectively), but this i.p. therapy cannot be recommended as standard therapy owing to its high toxicity. It is not surprising that there is a difference in antitumor efficacy and toxicity between the i.p. and i.v. groups because patients in the i.p. group received a high dose of carboplatin in addition to an already high dose of cisplatin.

(3) In the GOG172 study,[4] the administration of paclitaxel (i.v.) + cisplatin (i.v.) and paclitaxel (i.v.) + cisplatin (i.p.) + paclitaxel (i.p.; Day 8) was examined in 417 cases of ovarian cancer stage III (residual tumor diameter < 1 cm). It was reported that the i.p. group had a significant lengthening of PFS compared with the patient group receiving i.v. therapy (24 *vs.* 19 months, respectively) and the i.p. group exhibited a significantly lower recurrence risk (0.73 *vs* 1, respectively). However, as in the previous study, the concentrations of the chemotherapeutic agents used in the i.p. group were high. Therefore, the results cannot be simply compared, making the determination of an advantage of one treatment regimen over the other difficult.

The interpretations of treatment results from the above representative i.p. chemotherapies are divided and no uniform opinion has been established. It has also been pointed out that the control groups did not receive paclitaxel + carboplatin, the present standard therapy. In addition, there are complications specific to i.p. therapy, such as abdominal pain due to peritoneal stimulation and blockage of the intravenous catheter, local inflammation, and, although infrequent, intestinal perforation.[5) 6)] It is necessary to practice caution in the management of such chemotherapy. There are also questions regarding the optimal dose of chemotherapeutic agents administered and the uniformity of drug diffusion at the sit of contact on the surface of tumor cells.

Table 13 Reports on Intraperitoneal Chemotherapy

Authors/study	No. cases	Chemotherapeutic agents	Results
Alberts[2)] (SWOG8501, GOG, ECOG)	654	Cisplatin (i.v.) 100 mg/m^2 + cyclophosphamide (i.v.) 600 mg/m^2 *vs.* Cisplatin (i.p.) 100 mg/m^2 + cyclophosphamide (i.v.) 600 mg/m^2, every 3 weeks, six cycles	MST (i.v. *vs.* i.p.): 41 *vs.* 49 months
Markman[3)] (GOG114 SWOG, ECOG)	462	Cisplatin (i.v.) 75 mg/m^2 + taxol (iv) 135 mg/m^2 *vs.* Carboplatin (i.v.) AUC = 2, every 4 weeks, two cycles → taxol (i.v.) 135 mg/m^2 + cisplatin (i.p.) 100 mg/m^2, every 3 weeks, six cycles	PFS (i.v. *vs.* i.p.): 22 *vs.* 28 months OS (i.v. *vs.* i.p.): 52 *vs.* 63 months
Armstrong[4)] (GOG172)	417	Taxol (i.v.) 135 mg/m^2 + cisplatin (i.v.) 75 mg/m^2 *vs.* Taxol (i.v.) 135 mg/m^2 + cisplatin (i.p.) 100 mg/m^2 + taxol (i.p.) 60 mg/m^2 (Day 8) every 3 weeks, six cycles	PFS (i.v. *vs.* i.p.): 19 *vs.* 24 months

MST, median survival time.

I. Other Chemotherapy: High-Dose Chemotherapy

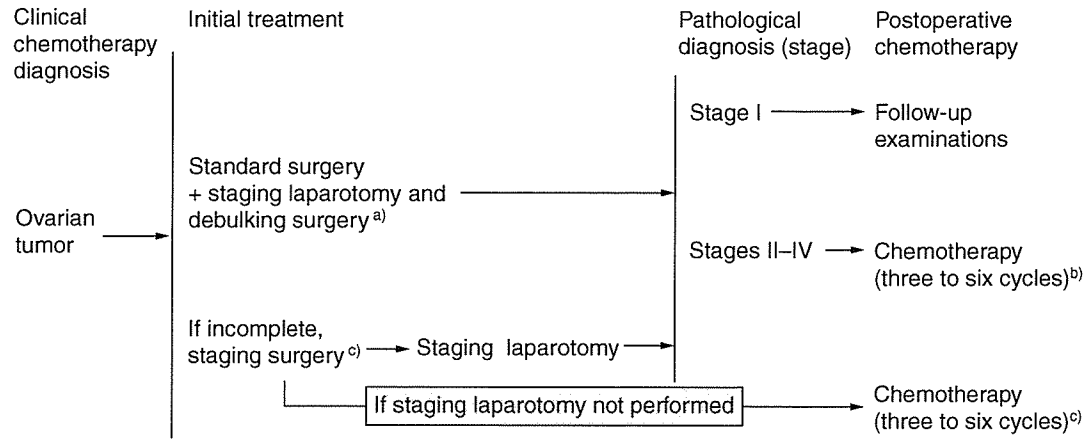
It is possible to use high-dose chemotherapy with concomitant PBSCT, in which the doses are five- to 10-fold greater than normal doses used. However, there are no reports of improved therapy results using high-dose chemotherapy **[III, C]**.

Remarks

A high efficacy rate has been reported for high-dose chemotherapy with PBSCT.[1] There are only a few reports of long-term prognostic results using this treatment regimen: specifically, a 4-year survival rate of 62% and a 4-year DFS rate of 57% in stages III and IV ($n = 20$)[2] and 5-year survival rates of 58.1% and 33.7% for stage III ($n = 46$) and stage IV ($n = 19$), respectively.[1] However, a randomized, controlled study is necessary in order to evaluate the true effectiveness of this treatment regimen. A further increase in therapeutic effects may be achieved by increasing the dose intensity above a certain amount. In other words, one cannot negate the existence of the 'second threshold' of dose.[3] At the present time, high-dose chemotherapy is at the stage of an experimental treatment.[4]

Ⓥ Treatment of Borderline (Epithelial) Tumors: Flowchart and Explanations

A. Treatment Flowchart



a) Intraperitoneal staging laparotomy is as in ovarian cancer. For retroperitoneal lymph node treatment, refer to the explanations below. If preservation of fertility is desired, refer to p. 22.
b) Three to six cycles of chemotherapy are as in epithelial ovarian cancer. For clinical efficacy, refer to the explanations below.
c) If no residual tumor is suspected at the end of staging laparotomy, it is possible to provide only follow-up examinations.

B. Explanation of Flowchart

a. If a diagnosis of borderline tumor is made by rapid intra-operative histological diagnosis during surgery for intrapelvic tumor, standard surgery and staging laparotomy, or primary debulking surgery, is performed as in ovarian cancer [**III, A'**]. For stage I, unilateral adnexectomy and intraperitoneal biopsy are performed with follow-up examinations, but without postoperative chemotherapy[1)~4)] [**III, B**]. For stages II–IV, three to six cycles of postoperative chemotherapy are performed [**III, C**]. However, when a diagnosis of borderline tumor by rapid intra-operative histological diagnosis is difficult, it is necessary to make a diagnosis from permanent tissue sections. Retroperitoneal lymph node biopsy (dissection) of borderline tumor, especially mucinous tumor, is not considered to affect the prognosis[2) 5)] [**III, B**]. Cases in which the tumor has been determined to have progressed beyond the ovary following intraperitoneal examination should be managed as in ovarian cancer.

b. For visual residual tumor, three to six cycles of postoperative chemotherapy are performed, as in ovarian cancer therapy [**III, C**]. However, there is no proven usefulness of adjuvant chemotherapy for borderline tumor[4) 6)~8)] [**III, B**].

c. If insufficient staging is performed at surgery, it is advisable to reoperate to perform staging laparotomy [**III, B**]. If no reoperation is performed and a residual lesion is suspected, three to six cycles of postoperative chemotherapy are performed [**III, C**]. In some cases, it is possible to omit chemotherapy if no residual tumor is suspected [**III, C**].

Ⅵ Follow up After Initial Treatment

A. Intervals for Office Visits [IV, E]

Time post-treatment	Follow up
~ 1 year	Every 1–2 months
~ 2 years	Every 2–3 months
~ 3 years	Every 3–4 months
~ 5 years	Every 4–6 months
≥ 5 years	Every 6–12 months

Remarks

There is no established optimal follow-up interval after the initial treatment for ovarian cancer and there is insufficient scientific basis to establish such a standard. Generally, a prudent follow up is performed for 5 years post-treatment to enable early detection of any recurrent cancer.

Additional Statements:

(1) According to an NIH consensus statement, follow-up examinations should be performed every 3–4 months within 2 years after the initial treatment, and at longer intervals after 2 years. The NCCN guidelines[1] also state similar intervals for follow-up examinations.

(2) In contrast, Kouno *et al.*[2] established a more conservative standard for follow-up examinations: monthly for the first 2 years and every 2 months after 2 years.

(3) There is a high probability of recurrence for stages III and IV advanced cancer within 2 years after treatment. It has been reported that recurrence rates are approximately 20% within 1 year, approximately 50% within 2 years, and approximately 60% within 3 years.[3]

B. Medical Examinations and Tests [IV, E]

Examinations and tests	Interval
Pelvic and external examination, medical history consultation	Every visit
Tumor markers, such as CA125	Every visit
Transvaginal or transabdominal ultrasonography	Every 3–6 months
Abdominal CT or MRI	Every 6 months; after 2 years, every 12 months
Chest X-rays	Every 12 months
Ga scintigraphy, bone scintigraphy, IVP, laparoscopy	If appropriate

CT, computed tomography; MRI, magnetic resonance imaging; IVP, intravenous pyelography.

Remarks

It is difficult to find a strong scientific basis for suggesting the most appropriate medical examinations and tests to be performed at follow up after initial ovarian cancer therapy. Generally, the recommended examinations are mainly external, pelvic, and ultrasonographic, as well as measurements of tumor markers, such as CA125 (see below). This is one standard, but the selection of examinations, tests performed, and the time intervals should be determined on the basis of a comprehensive consideration of stage, a variety of prognostic factors, and the type of treatment administered.

Additional Statements:

(1) The NIH and NCCN recommend examinations, mainly external and pelvic, and measurement of the tumor marker CA125 as the most basic items for consideration that cannot be omitted.

(2) Ultrasonographic examination is a simple, non-invasive examination that is performed on an out-patient basis. Therefore, if there are suspicious findings during the medical examination, ultrasonography should be performed.

(3) It is advisable to perform abdominal computed tomography (CT) and magnetic resonance imaging (MRI), as well as chest X-rays, every 0.5–1 years.

(4) If possible, Ga scintigraphy, bone scintigraphy, intravenous pyelography (IVP), and laparoscopy should be performed as needed.

Regarding CA125:

(1) CA125 is the most sensitive marker for non-mucinous epithelial ovarian cancer and is also useful in detecting cancer recurrence.

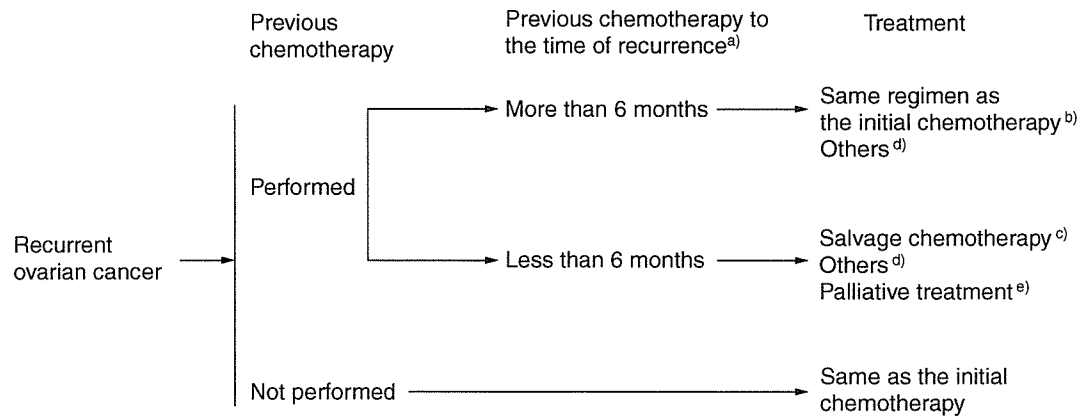
(2) Over 80% of recurrent cases test positive when the cut-off value for CA125 is set at 35 U/mL.[4)~6)]

(3) Bilateral salpingo-oophorectomy is generally performed in many cases of ovarian cancer and many opinions state that the cut-off value for CA125 should be set at the same value as that for post-menopausal patients.[7)~10)] Gard and Houghton[8)] and Sugiyama *et al.*[10)] stated that the cut-off value for CA125 should be 15 and 16 U/mL, respectively.

(4) There have been studies that have monitored changes in CA125 values over time for the early diagnosis of cancer recurrence.[6) 11)] It has been reported that recurrence is highly suspected in cases where the value of CA125 rises over 25 U/mL in 1 month[6)] or when the value increases upon measurement more than two consecutive times.[11)]

Ⅶ Treatment for Recurrent Ovarian Cancer: Flowchart and Explanations

A. Treatment Flowchart



B. Explanation of Flowchart

a) Sensitivity to platinum agents.

Generally, for recurrent ovarian cancer, subjects are those who have received platinum agents as the key drug at initial chemotherapy. Therefore, the key point in the selection of a chemotherapeutic agent will be the time interval between the initial chemotherapy and recurrence, namely the platinum-free interval (PtFI). Secondary chemotherapy is considered to be more efficacious the longer the PtFI. In general, recurrence within 6 months after the completion of initial chemotherapy constitutes a platinum-resistant case.[1) 2)] Taxane is also evaluated in the same way.[3)]

b) Chemotherapy for platinum-sensitive recurrent ovarian cancer.

Generally, the recommendation for platinum-sensitive tumors in patients in which more than 6 months has elapsed since the completion of the initial chemotherapy is the same regimen as the initial chemotherapy or concomitant therapy of platinum- and taxane-based anticancer agents[3)~6)] **[II, A]**.

c) Salvage chemotherapy **[III, C]**.

Chemotherapy for platinum-resistant recurrent ovarian cancer. Reports of the efficacy of various chemotherapeutic agents are limited to efficacy rates from phase II studies for ovarian cancer recurring within less than 6 months after completion of the previous chemotherapy. The salvage chemotherapy described below is recommended for platinum-resistant recurrent ovarian cancer. The following doses and dose intervals are estimations based on overseas reports and Japanese usage and dose provisions. It is also necessary to modify treatment for women in Japan depending on the patient's overall condition. Among the drugs that are reported to be effective for ovarian cancer, only carboplatin, cisplatin, paclitaxel, docetaxel, and irinotecan are covered by insurance in Japan.

The main chemotherapies and typical doses used at present, at the clinical-study level, in Japan are given in Table 14.

Table 14 Chemotherapy for Recurrent Ovarian Cancer

Paclitaxel[7)~10)]
Paclitaxel 180–210 mg/m^2, Day 1; 21-day interval
Or
Paclitaxel 80 mg/m^2, Days 1, 8, 15; 21-day interval
Paclitaxel + carboplatin[11)]
Paclitaxel 60–80 mg/m^2, Days 1, 8, 15 + carboplatin AUC = 2, Days 1, 8, 15; 28-day interval
Docetaxel[12)~14)]
Docetaxel 70 mg/m^2, Day 1; 21-day interval
Irinotecan[15) 16)]
Irinotecan 100 mg/m^2, Days 1, 8, 15; 28-day interval[15)]
Or
Irinotecan 300 mg/m^2, Day 1; 28-day interval*[16)]
Etoposide p.o.[17)] (not covered by insurance in Japan)
Etoposide 50 mg/m^2, Days 1–21; 28-day interval
Gemcitabine[18)] (not covered by insurance in Japan)
Gemcitabine 800–1000 mg/m^2, Days 1, 8, 15; 28-day interval[19)]
Cisplatin + etoposide p.o.[20) 21)] (not covered by insurance in Japan)
Cisplatin: 60 mg/m^2, Days 1, 8, 15 + etoposide 50 mg/m^2, Days 1–14; 28-day interval
Docetaxel + Irinotecan[22) 23)]
Docetaxel 60 mg/m^2, Day 8 + irinotecan 60 mg/m^2 every day 1, 8; 21-day interval[22)]
Or
Docetaxel 60 mg/m^2, Day 1 + irinotecan 200 mg/m^2, Day 1; 21-day interval*[23)]

*Usages and doses given are according to overseas reports.

d) Other treatments.

(1) Clinical studies.

The main objectives of treatment for recurrent ovarian cancer are an improvement in survival rate and maintenance of QOL in patients with either platinum-sensitive or -resistant recurrent ovarian cancer. Clinical studies should be designed to thoroughly examine these above objectives and be granted approved by an IRB.

(2) Radiation therapy.

Radiation therapy for recurrent ovarian cancer is indicated mainly for platinum-resistant or chemotherapy-resistant tumors.[2] Radiation therapy should be limited to cases in which there is only a local recurrence and the subject's overall condition is favorable **[III, B]**.

(3) Cytoreductive therapy.

There is no clear evidence of significant prognostic improvement from cytoreductive therapy. However, there is a report of cytoreductive surgery contributing to prognostic improvement in cases with a disease-free period of over 12 months and maximum residual diameter of < 1.5 cm.[2] Surgical indication for recurrent ovarian cancer should be considered only after thorough evaluation of the recurrent cancer **[III, A']**.

e) Palliative treatment.

Priority should be placed on maintenance of a patient's QOL in recurrent ovarian cancer. Physicians should be proactive about any complaints, especially of pain[24] **[IV, A']**.