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Review Article

Current status of chemotherapy in risk-adapted management for metastatic testicular germ cell cancer

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Today, approximately 80% of men with metastatic testicular cancer can be cured with chemotherapy combined with the appropriate surgery. The improved treatment outcome has led to the stratification of patients with metastatic disease by the consensus prognostic index; the International Germ Cell Cancer Consensus Group classification. Currently, the first-line chemotherapy with bleomycin, etoposide, and cisplatin (BEP) remains the standard management of metastatic testicular cancer. Three cycles of BEP for good-prognosis patients and four cycles of BEP for intermediate- and poor-prognosis patients are the standard first-line chemotherapy. To achieve the optimal outcome, BEP should be given with appropriate supportive care and risk assessment for toxicity. Although no universal prognostic criteria have been defined for the recurrent or refractory disease, the risk-adapted approach may clarify the role of ifosfamide- and paclitaxel-containing conventional-dose chemotherapy or high-dose chemotherapy in the second-line setting. Several investigators reported recent improvement of treatment outcome of testicular cancer patients, especially those with poor prognosis. Along with the progress in chemotherapy, the risk-adapted management at experienced hospitals seems to be responsible for the recent progress in treatment outcome. (*Cancer Sci* 2010; 101: 22–28)

Germ cell cancers most commonly arise in the testes. Testicular germ cell cancers are separated into two histological types: seminoma and non-seminoma. The latter type is more aggressive, and more often requires chemotherapy and surgery for treatment of metastatic disease. Testicular cancer is relatively rare, but it is the most common cancer in men between the ages of 15 and 35 years. Although an increase is noted in Western countries, the incidence of testicular cancer in Japan has remained comparatively low.[1–6]

The outcome of metastatic testicular cancer treatment has improved substantially since the introduction of cisplatin, vinblastine, and bleomycin (PVB) in the 1970s.[7] Subsequently, randomized clinical trials comparing bleomycin, etoposide, and cisplatin (BEP) to PVB demonstrated that the BEP regimen had a lower toxicity and higher cure rate.[8] Therefore, BEP has been the standard first-line chemotherapy since the mid 1980s. Today, approximately 80% of men with metastatic testicular cancer can be cured with chemotherapy combined with the appropriate surgery. The improved treatment outcome has led to the stratification of patients with metastatic disease by prognosis. However, differences among prognostic classification systems made it difficult to compare the results of clinical trials,[9–13] leading the International Germ Cell Cancer Consensus Group (IGCCCG) to publish a consensus prognostic index for metastatic germ cell cancers in 1997.[14] The IGCCCG classification (Table 1) uses the primary site, presence of non-pulmonary visceral metastases, and tumor markers human chorionic gonadotropin, α-fetoprotein, and lactate dehydrogenase as prognostic factors. The IGCCCG classification is simple and highly reproducible, and therefore, is used both for risk-stratified clinical trials and in standard management to select the appropriate chemotherapy. It is also useful in evaluation of the outcome of each treatment institution.

Several investigations, including those from Japan, reported improvement in treatment outcome.[15–20] The potential explanations are the widespread use of first-line chemotherapy with BEP and improvement of second-line treatment. In this review, we will summarize the recent risk-stratified clinical trials in first-line chemotherapy and second-line chemotherapy, and also discuss the risk assessment for toxicity of BEP.

First-line chemotherapy for good-risk metastatic disease

Based on the IGCCCG data, approximately 60% of metastatic germ cell cancers are allocated to the good-prognosis group, and the expected cure rate is approximately 90%. Therefore, clinical chemotherapy trials for patients with good-risk disease have focused on attempts to reduce the toxicity of the standard chemotherapy of four cycles of BEP[8] without compromising efficacy. The standard BEP regimen consists of 100 mg/m^2 cisplatin, 500 mg/m^2 etoposide, and 90 U bleomycin per cycle, repeated every 21 days. The trials of risk-adapted management for good-risk patients began before the development of the IGCCCG classification. One approach was elimination of bleomycin to avoid pulmonary toxicity. In 1987, investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) published the results of a randomized clinical trial (RCT)[21] for good-risk patients as defined by the MKSCC criteria. The study showed that four cycles of a two-drug combination, etoposide and cisplatin (EP), were therapeutically equivalent to and less toxic than three cycles of a five-drug regimen consisting of cyclophosphamide, vinblastine, bleomycin, dactinomycin, and cisplatin (VAB-6). The approach of the Indiana University group was simply to delete one cycle of BEP.[22] The Southeastern Cancer Study Group demonstrated that three cycles of BEP had less toxicity than and equivalent efficacy to four cycles of BEP for good-risk patients as defined by Indiana University criteria. Because carboplatin was expected to be less toxic than cisplatin, two RCT substituting carboplatin for cisplatin, with two- or three-drug combination regimens, were conducted but the regimen including carboplatin showed significantly poorer progression-free survival.[23,24] Table 2 summarizes the more recently published RCT studies. The Eastern Cooperative Oncology Group compared three cycles of EP with three cycles of BEP in an attempt to further reduce toxicity.[25] Overall, 94% of patients receiving BEP achieved disease-free status, compared with 88% of those receiving EP. Both the failure-free survival and overall

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Table 1. International Germ Cell Cancer Consensus Group (IGCCCG) classification of metastatic germ cell cancers

	Non-seminoma	Seminoma
Good prognosis	Testis/retroperitoneal primary	Any primary site
	No non-pulmonary visceral metastasis	No non-pulmonary visceral metastasis
	Good markers	Normal AFP, any hCG, any LDH
	5-year PFS 89%, 5-year OS 92%	5-year PFS 82%, 5-year OS 86%
Intermediate prognosis	Testis/retroperitoneal primary	Any primary site
	No non-pulmonary visceral metastasis	Non-pulmonary visceral metastasis
	Intermediate markers	Normal AFP, any hCG, any LDH
	5-year PFS 75%, 5-year OS 80%	5-year PFS 67%, 5-year OS 72%
Poor prognosis	Mediastinal primary or	No patient classified as poor-prognosis
	Non-pulmonary visceral metastasis	
	Poor markers	
	5-year PFS 41%, 5-year OS 48%	

Marker criteria for non-seminoma patients	Good	Intermediate	Poor
AFP	<1000 ng/mL	>1000 ng/mL and <10 000 ng/mL	>10 000 ng/mL
hCG	<5000 IU/L	>5000 IU/L and <50 000 IU/L	>50 000 IU/L
LDH	<1.5× ULN	>1.5× ULN and <10× ULN	>10× ULN

AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

survival were significantly lower with three cycles of EP. The European Organization for Research and Treatment of Genitourinary Tract Cancer (EORTC) group study compared four cycles of BEP with four cycles of EP using a dose of etoposide reduced to 360 mg/m^2 per cycle.[26] Although there was no significant difference in time to progression and overall survival, the complete response rate to BEP was significantly better than that to EP (95% and 87%, respectively). Similarly, the Australian and New Zealand Germ Cell Trial Group compared the original three cycles of BEP and four cycles of a modified BEP regimen with reduced doses of bleomycin (30 U per cycle) and etoposide (360 mg/m^2 per cycle).[27] Toner *et al.* reported that the overall survival rate was substantially better with the original BEP regimen. The reduction in both the total dose of bleomycin and the dose intensity of etoposide may be responsible for the poorer outcome.[27] The definition of good-risk at the start of the study was based on MSKCC criteria. When the patients were reclassified according to the IGCCCG classification, 83% of patients were defined as good prognosis. The survival benefit of the original three cycles of BEP remained significant if only IGCCCG-defined good-prognosis patients are considered. Taken together, these studies demonstrated that bleomycin could not be omitted or reduced without compromising treatment outcome when treatment was limited to three cycles or the dose of etoposide was reduced.

In 1995, the EORCT and Medical Research Council (MRC) began a large RCT that compared three cycles of BEP and three cycles of BEP with a fourth cycle of EP.[28] The study detected a 5% difference favoring the four-cycle regimen. This is the only RCT for good-prognosis patients that used the IGCCCG classification as the eligibility criterion. There was no significant difference in progression-free survival; it was 90% on the three-cycle regimen and 89% on the four-cycle regimen. The study confirmed that three cycles of BEP is sufficient treatment for good-prognosis patients.[28] Recently, the MSKCCC group reported a large retrospective analysis of four cycles of EP for 289 patients with good-prognosis disease as defined by the IGCCCG classification. Four cycles of EP with surgical resection of residual disease achieved 98% complete remission with only 6% relapse. The 5-year overall survival was 96% with a median follow up of 7.7 years.[29] Both studies showed that two regimens, three cycles of BEP or four cycles of EP, were still optimal chemotherapy for good-risk patients, as defined by the IGCCCG classification. A controversy remained on which regimen was preferred. The Genito-Urinary Group of the French Federation of Cancer Centers (GETUG) conducted an RCT to compare three cycles of BEP and four cycles of EP for patients with good-prognosis non-seminoma.[30] This is the only study so far to directly compare the two optional regimens mentioned above. Although the risk definition was originally made by the Institut Gustave Roussy (IGR) prognostic criteria, the patients were retrospectively assigned to the IGCCCG classification. The 4-year event-free survival rates were 91% in the three cycles of BEP arm and 86% in the four cycles of EP arm. The 4-year overall survival rates were 96 and 92%, respectively. Although there was no significant difference in the endpoints, the authors pointed out that a statistically non-significant trend toward more relapse and deaths remained when considering good-prognosis patients defined by the IGCCCG classification. The authors concluded that the standard treatment is three cycles of BEP for non-seminoma patients with good prognosis according to the IGCCCG classification.[30]

First-line chemotherapy for poor-risk metastatic disease

The efficacy of four cycles of BEP for poor-risk metastatic disease was demonstrated by a RCT that compared it with four cycles of PVB. The subgroup analysis for patients with advanced disease according to Indiana University criteria demonstrated that the complete response rates to BEP and PVB were 63% and 38%, respectively.[8] The benefit of replacing vinblastine with etoposide in first-line chemotherapy was confirmed by another RCT comparing four cycles of BEP with two cycles of BEP and two cycles of PVB.[31] Since then, the four cycles of BEP regimen has been recognized as the standard treatment for comparison with the outcome of subsequent experimental treatments for poor-risk patients. In an earlier attempt to improve efficacy by increasing the dose intensity of cisplatin, the National Cancer Institute demonstrated that a regimen including etoposide, vinblastine, bleomycin, and a double dose of cisplatin (200 mg/m^2 per cycle) was superior to the PVB regimen.[32] However, the benefit of the cisplatin dose intensity was not

confirmed by subsequent RCT that compared the standard BEP regimen with BEP using the double dose of cisplatin.[33]

In the past decade, several approaches were tested to improve the outcome of poor-risk patients, which included introduction of a new active drug, dose-dense chemotherapy alternating with a multidrug regimen, and high-dose chemotherapy (HDCT) with autologous stem-cell rescue. The selected RCT studies for poor-risk patients are summarized in Table 3. Nichols *et al.* conducted a large intergroup trial to test the efficacy of introduction of ifosfamide into the first-line chemotherapy.[34] In this trial, nearly 300 poor-risk patients defined by Indiana University criteria were randomly assigned to receive either four cycles of BEP or four cycles of etoposide, ifosfamide, and cisplatin (VIP). The BEP and VIP regimens produced comparable durable response rates of approximately 60%, and there was no significant difference in failure-free survival and overall survival between the two arms. However, VIP was associated with more hematological toxicity than BEP. The MRC/EORTC groups compared four cycles of BEP and two additional cycles of EP (BEP/EP) with an experimental regimen of three cycles of schedule-dense bleomycin, vincristine, and cisplatin followed by two cycles of VIP combined with bleomycin (BOP/VIP-B).[35] Kaye *et al.* reported that the intensive BOP/VIP-B regimen was associated with more hematological toxicity but with no evidence of improvement in treatment outcome.[35] Thus, those studies did not support the routine introduction of ifosfamide to first-line chemotherapy. However, reanalysis of the intergroup trials revealed that the VIP regimen may be considered a treatment alternative for patients having risks factors for bleomycin pulmonary toxicity. Hinton *et al.* retrospectively reclassified the patients by the IGCCCG classification and updated the data with a median follow up of 7.3 years.[36] In the subset of patients defined as poor prognosis with IGCCCG classification, neither progression-free survival (VIP 56% *vs* BEP 49%) nor overall survival (VIP 62% *vs* BEP 57%) was significantly different. The reanalysis showed increased hematological toxicity for the VIP arm, but it did not result in an increased risk of neutropenic infection or life-threatening bleeding.[36]

The GETUG group compared four cycles of BEP and dose-dense chemotherapy with four to six alternating cycles of cyclophosphamide, doxorubicin, cisplatin (CISCA) and vinblastine and bleomycin (VB).[37] The study used IGR prognostic criteria as the eligibility criteria. There was no significant difference in response and survival between the two arms. A benefit of the dose-dense chemotherapy was not revealed even when analysis was limited to 115 poor-prognosis patients according to the IGCCCG classification. As possible explanations for the modest result, the authors pointed out the lower cisplatin density and absence of etoposide in the CISCA/VB arm.[37] The benefit of HDCT with autologous stem-cell rescue has been examined in RCT studies. The GETUG group conducted a RCT comparing four cycles of bleomycin, etoposide, vinblastine, and double-dose cisplatin ($BEP_{200}V$) and two cycles of $BEP_{200}V$, followed by HDCT including etoposide, cyclophosphamide, double-dose cisplatin (PEC).[38] The durable response rates were similar in both arms, but there was a trend toward inferior overall 5-year survival and more hematological toxicities in patients who received HDCT. The HDCT trial conducted in the USA is the only published RCT that used the IGCCCG criteria to define poor-risk patients.[39] Of the 219 patients, 174 (79%) were defined as having a poor prognosis, and 45 (21%) had an intermediate prognosis. The patients received either four cycles of BEP or two cycles of BEP followed by two cycles of high-dose carboplatin, etoposide, and cyclophosphamide (HD-CEC).[39] The 1-year durable response rate was 52% in the BEP arm, and 48% in the HD-CEC arm. As expected, the toxicity was more severe in the HD-CEC arm. The 1-year durable response rate (46% and 48%) and 2-year survival rate (69% and 67%) were similar in both arms in the subset of patients with poor prognosis. However, the unplanned subgroup analysis for unsatisfactory marker decline showed a higher 1-year durable complete response in patients who received HD-CEC compared with patients receiving only BEP (61% and 34%, respectively). Although further investigation is needed, patients with slow marker decline may benefit from high-dose chemotherapy. A Japanese multicenter single-arm study examined the activity of HDCT for patients with elevated tumor markers after three cycles of BEP. The HDCT regimen consisted of ifosfamide, carboplatin, and etoposide.[40] The 5-year survival of 24 patients who received HDCT was 63%. A RCT introducing tumor marker decline after one cycle of BEP as risk criteria is now being carried out by the GETUS groups.

In addition, several phase II studies for patients with poor prognosis as defined by the IGCCCG classification showed promising results. A German group investigated the activity of high-dose VIP (HD-VIP) with stem-cell rescue with promising results.[41] Recently, Hartmann *et al.* tested the efficacy and safety of introducing a conventional dose of paclitaxel into the HD-VIP regimen.[42] Overall, 41 patients with poor prognosis were treated with HD-VIP combined with paclitaxel. The calculated 2- and 5-year survival rates were 78% and 75% respectively. Investigators at the Royal Marsden Hospital developed a dose-dense sequential regimen including carboplatin, bleomycin, vincristine, and cisplatin, followed by BEP (CBOP/BEP).[43] The reported 5-year progression-free survival and overall survival for 45 patients with poor prognosis was 83%

Table 2. Randomized trials of first-line chemotherapy in patients with good-risk metastatic disease

Source	No. patients	Risk system (%)	Regimens (%)	PFS	OS	Conclusion
Loehrer *et al.*[25]	171	Indiana[11]	BEP × 3	86†	95	BEP superior
			EP × 3	69	86	
de Wit *et al.*[26]	395	MRC/EORTC[12]	BE360P × 4	93	97	BEP superior
			E360P × 4	90	94	
Toner *et al.*[27]	166	MSKCC[10]	BEP × 3	90	96	BEP superior
			mBEP × 4	81	84	
de Wit *et al.*[28]	792	IGCCCG[14]	BEP × 3	90	97	Equivalent efficacy
			BEP × 3 + EP × 1	89	97	
Culine *et al.*[30]	257	IGR[13]	BEP × 3	91‡	96	Equivalent efficacy
			EP × 4	86	92	

†Failure-free survival; ‡event-free survival. E360, etoposide reduced to 360 mg/m^3 per cycle; mBEP, modified BEP (bleomycin reduced to 30 U per cycle; etoposide reduced to 360 mg/m^3 per cycle); OS, overall survival; PFS, progression-free survival; MRC, Medical Research Council; EORTC, European Organization for Research and Treatment of Cancer; MSKCC, Memorial Sloan-Kettering Cancer Center; IGCCCG, International Germ Cell Cancer Consensus Group; IGR, Institut Gustave Roussy.

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Table 3. Randomized trials of first-line chemotherapy in patients with poor-risk metastatic disease

Source	No. patients	Risk system (%)	Regimens (%)	PFS	OS	Conclusion
Nichols *et al.*[34]	286	Indiana[11]	BEP × 4	60†	71	VIP not superior and more toxic
			VIP × 4	64	74	
Kaye *et al.*[35]	271	MRC/EORTC[12]	BEP × 4/EP × 2	60†	76	BOP/VIP-B not superior and more toxic
			BOP × 3 + VIP-B × 2	53	69	
Culine *et al.*[37]	185	IGR[13]	BEP × 4	47‡	69	CISCA/VB not superior and more toxic
			CISCA/VB × 4–6	37	59	
Droz *et al.*[38]	114	IGR[13]	$BEP_{200}V \times 4$	54	75	HD-PEC not superior and more toxic
			$BEP_{200}V \times 2$ + HD-PEC × 2	47	61	
Motzer *et al.*[39]	174	IGCCCG[14]	BEP × 4	46§	69	HD-CEC not superior and more toxic
			BEP × 2 + HD-CEC × 2	48	67	

†Failure-free survival; ‡event-free survival; §1-year durable response rate. $BEP_{200}V$, bleomycin, etoposide, vinblastine, and double-dose cisplatin; BOP/VIP-B, bleomycin, vincristine and cisplatin/VIP combined bleomycin; CEC, carboplatin, etoposide, and cyclophosphamide; CISCA/VB, cyclophosphamide, doxorubicin, cisplatin/vinblastine, bleomycin; HD, high dose; OS, overall survival; PEC, etoposide, cyclophosphamide, and double-dose cisplatin; PFS, progression-free survival.

and 88%, respectively. Because of the promising result, a phase III study comparing BEP and C-BPO/BEP is now ongoing.[43]

Taken together, the available evidence from randomized studies failed to demonstrate any advantage over four cycles of BEP for intermediate- and poor-risk patients.

Completion and risk assessment for toxicity of BEP

Today, chemotherapy with BEP remains the standard management of metastatic testicular cancer. To achieve the optimal outcome, BEP should be given without dose reduction at 3-week intervals to the extent possible. Several investigators demonstrated that maintaining the relative dose intensity (RDI) of first-line chemotherapy is an important principle for optimal response.[44,45] The European Germ Cell Cancer Consensus Group recommended that postponing treatment, at a maximum of 3 days for each decision, should only be considered in cases of existing fever, neutrophil counts $<500/mm^3$, or platelet counts $<100\,000/mm^3$ at day 1 of the subsequent cycle.[46] Since the development of BEP in the 1980s, there has been a considerable advance in supportive therapies, such as granulocyte colony-stimulating factor (G-CSF) and 5-hydroxytryptamine-3 (5-HT3) serotonin receptor antagonist. Recently, we re-evaluated the completion and toxicity of BEP combined with modern supportive care in 42 Japanese patients.[47] Overall, the subsequent chemotherapy could be started within 3 days of postponement in 83 of 93 treatment cycles (89%). Dose reduction or drug elimination was needed in only three patients. As a result, treatment with an RDI over 0.9 was carried out in 88% of patients. The average RDI of bleomycin was 0.95, and those of etoposide and cisplatin were 0.97. This is in accordance with our previous analysis of RDI for PVB, where RDI increased from 0.87 to 0.98 with use of G-CSF.[45] Today, the routine use of G-CSF in testicular cancer chemotherapy is approved by the Japanese government. An improvement of RDI in BEP or EP was reported in a prospective study in which subjects were randomized to receive or not receive G-CSF.[48] The randomized study showed that the routine use of G-CSF significantly improved the delivery of the planned treatment schedule. The median RDI for cisplatin, etoposide, and bleomycin were 1.00, 0.99, and 0.98, respectively.[48]

In our series, two patients developed clinically evident bleomycin pulmonary toxicity, but recovered with discontinuation of bleomycin. Chest computed tomography revealed that three additional patients, although lacking signs and symptoms, had abnormalities suggesting bleomycin pulmonary toxicity. It is of note that the median age of these three patients was 43 years, which is relatively old among testicular cancer patients.[47] Bleomycin pulmonary toxicity and neutropenic sepsis are the leading causes of treatment-related death of BEP. The reported incidence of fatal bleomycin pulmonary toxicity is 0.8–2.8%.[8,48,49] The risk is known to be closely related to the cumulative bleomycin dose. The incidence of bleomycin pulmonary toxicity rises to 13–17% when the cumulative dose is more than 450 U.[50] Nonetheless, attention should be paid to any patient developing respiratory symptoms even after a lower dose of bleomycin, particularly if the patient has other risk factors for bleomycin pulmonary toxicity. Impaired renal function is another important risk factor, because bleomycin is cleared by renal excretion. Several investigators, including us, reported that a decline of renal function could be a significant risk factor for development of bleomycin pulmonary toxicity.[49,51,52] Age is the next most important risk factor.[49,53] Simpson *et al.* reported a high incidence of fatal bleomycin pulmonary toxicity, approximately 10%, in testicular cancer patients over 40 years old with a mean cumulative bleomycin dose of 180–210 U.[49] To avoid fatal bleomycin toxicity, several investigators pointed out that BEP can be replaced by other suitable regimens in patients with unacceptable risks for this complication. Evidence from RCT suggested that four cycles of EP for good-risk patients[30,54] or four courses of VIP for intermediate- or poor-risk patients[36] is preferred to BEP to avoid bleomycin toxicity.

Salvage chemotherapy for recurrent or refractory disease

Between 70% and 80% of patients with metastatic testicular cancer achieve a durable complete response with first-line chemotherapy alone or combined with surgery for residual mass. The remaining patients require salvage chemotherapy for recurrent or refractory disease after first-line treatment. Because these patients have a chance of cure, the second-line chemotherapy should be given with curative intent. Two different strategies have been evaluated: conventional-dose chemotherapy including other active drugs not previously used or HDCT with autologous

Table 4. Treatment outcomes with second-line standard dose chemotherapy

Source	Design patients	*n* (%)	Regimens	PFS	Duration
McCaffrey *et al.*[56]	Retrospective	56	VeIP/VIP	23	52 months
Loehrer *et al.*[57]	Phase II	135	VeIP	24	4.7 years
Motzer *et al.*[61]	Phase I/II	30	TIP	73	33 months
Kondagunta *et al.*[62]	Phase II	46	TIP	65	2 years
Mead *et al.*[63]	Phase II	51	TIP	38	1 year

PSF, progression-free survival; TIP, paclitaxel, ifosfamide, and cisplatin.

stem-cell rescue. The combination of ifosfamide and cisplatin with either etoposide (VIP) or vinblastine (VeIP) showed efficacy as a third-line chemotherapy in the 1980s.[55] Subsequently, those regimens have been investigated as second-line chemotherapy. Table 4 summarizes the results of second-line chemotherapy including ifosfamide. The MSKCC group reported a retrospective analysis of 56 patients treated with VIP or VeIP.[56] The response rate and progression-free survival rate were 36% and 23%, respectively. In the largest series at Indiana University[57], 135 patients with progressive disease were treated with VeIP or VIP. Overall, 32 patients (24%) were continuously free of disease with a minimum follow up of 6 years. The cure rate was not satisfactory; however, both studies revealed that patients with testicular cancer had a better prognosis than patients with extragonadal germ cell tumor.[56,57] McCaffrey *et al.* reported that the 41% of patients with testicular cancer who relapsed after complete response to first-line therapy maintained a continuous disease-free status after VeIP or VIP.[56]

Paclitaxel showed antitumor activity with response rates of 11–25% in refractory or relapsed germ cell cancer patients in several single-agent phase II studies.[58,59] Paclitaxel also showed synergy with cisplatin and alkylating agents in *in vitro* studies using a cisplatin-resistant teratocarcinoma cell line.[60] Based on these preclinical and clinical data, the MSKCCC group introduced paclitaxel into second-line chemotherapy for testicular cancer patients. Forty-six patients with recurrent testicular cancer after a prior complete response were treated with paclitaxel, ifosfamide, and cisplatin (TIP) with routine G-CSF support.[61] Motzer *et al.* reported a response rate of 80%, and the progression-free survival was up to 73% with a median follow up of 33 months.[61] The results were confirmed in a subsequent study treating 46 patients with the same regimen.[62] The MRC group reported similar but somewhat inferior results with less-intensive TIP without the G-CSF support.[63] TIP has not been compared with other regimens by RCT, but the above results strongly suggested that a risk-adapted approach, selecting the intensity of treatment by patient risk, is useful in salvage chemotherapy. In Japan, the feasibility and efficacy of TIP or other conventional-dose regimens containing paclitaxel and ifosfamide were reported in testicular cancer patients who relapsed after first-line chemotherapy.[64,65]

HDCT has been investigated as salvage therapy since the 1980s. Initial studies of heavily pretreated patients were associated with significant morbidity and mortality.[66,67] In recent years, HDCT has been used more successfully even in the second relapse. Einhorn *et al.* published a large retrospective series including 184 patients treated with two cycles of VeIP, followed by two consecutive courses of high-dose carboplatin and etoposide between 1996 and 2004.[68] The treatment-related deaths were limited to three patients among the 184 patients. This is greatly due to the progress of support treatment and the accumulation of much experience at this institution. Overall, 63% of patients with various prognostic features achieved complete response without relapse with a median follow up of 4 years. In the study, 22 of 49 patients (45%) who received the treatment as third-line or later therapy remained disease free. The results indicated that testicular cancer patients are potentially curable with HDCT, even in the setting of third-line chemotherapy.[68]

In contrast, the role of HDCT as second-line chemotherapy remains controversial. A retrospective matched pair analysis based on prognostic factors estimated a 10% benefit in patients treated with high-dose chemotherapy as the second-line treatment compared with patients treated with conventional chemotherapy.[69] However, the only randomized trial conducted for second-line HDCT failed to show the superiority of HDCT over a conventional-dose regimen. Pico *et al.* reported a large RCT of 263 patients comparing four cycles of VIP with three cycles of VIP followed by a cycle of high-dose chemotherapy with carboplatin, etoposide, and cyclophosphamide.[70] The study included 220 patients (84%) with tumors of testicular origin and 98 patients (41%) with prior complete response to first-line chemotherapy. No significant improvement with HDCT was observed in either 3-year event-free survival (35% *vs* 42%) or overall survival (53% *vs* 59%).[70]

Recently, Kondagunta *et al.* reported the results of a risk-adapted approach in a second-line setting for patients who are likely to experience treatment failure with conventional-dose salvage chemotherapy.[71] A regimen of rapid recycling of paclitaxel and ifosfamide followed by high-dose carboplatin and etoposide (TICE) achieved continuous disease-free status in 51% of patients including extragonadal primary or progressive disease after incomplete response. When combined with the results of a similar study previously reported by the same group,[72] the TICE regimen achieved an overall complete response of 56%, with half of patients still alive with no evidence of disease.

Although there are no defined and universal prognostic criteria for the second-line setting such as the IGCCCG classification for the first-line chemotherapy, the risk-adapted approach may clarify the role of HDCT in the second-line setting. In Japan, a multicenter single-arm study that aims to test the efficacy of HDCT with nedaplatin and irinotecan for poor- and intermediate-prognosis patients with elevated tumor markers after four cycles of BEP is now ongoing. The two-drug combination at conventional doses has shown activity against refractory germ cell tumors.[73]

Recent treatment outcome of testicular cancer

Several investigations reported improvement in the outcome of testicular cancer patients treated in the most recent decade. Multiple factors, including the wide use of first-line therapy with BEP, introduction of intensified salvage chemotherapy, and surgery, may be responsible for this progress. In addition, several investigators pointed out the association between better treatment outcome, especially that of poor-prognosis patients, and the cumulative experience of the treatment institution.[74–76]

In Japan, the incidence of testicular cancer is much lower than in Western countries. Therefore, there are few specialized centers with high-volume experience comparable to those in Western countries. Most advanced testicular cancer patients in Japan are treated in university hospitals or regional cancer center urological oncology units rather than in highly specialized centers; therefore, it is important to examine the treatment outcome. Recently, Shintaku *et al.* analyzed the outcome of 296 patients with metastastic germ cell tumor treated between 1990 and 2001 at a cancer center hospital and six university hospitals in Japan, including our institution.[19] According to the IGCCCG classification, the 5-year overall survival of patients with non-seminoma tumors allocated to the good-, intermediate-, and poor-prognosis groups were 94%, 81%, and 61%, respectively. For metastatic seminoma, the 5-year overall survivals of the good- and intermediate-risk groups were 90% and 80%, respectively. There was a trend for survival to increase in all risk groups, in particular, a large increase in survival of patients with poor prognosis was observed. A large meta-analysis of metastatic non-seminoma patients treated after 1989 also showed remarkable improvement in survival, especially of patients with poor prognosis. In Japanese studies, the risk distribution was different from that of the IGCCCG data.[14] When limited to non-seminoma patients, 24%, 47%, and 29% of the patients allocated to the good-, intermediate-, and poor-prognosis groups survived. The proportion of patients with intermediate or poor prognosis is higher than that of the IGCCCG data (76% and 44%, respectively). Although there is a possibility that more Japanese patients are diagnosed at an advanced state, this may be due to

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the referral pattern of community hospitals to experienced hospitals. We have recommended that community hospitals refer advanced cases to our hospital.

Post-chemotherapy surgery, namely retroperitoneal lymph node dissection (RPLND), is an important part of metastatic testicular cancer management. Recent evidence supports close observation of residual retroperitoneal masses smaller than 3 cm in seminoma patients.[77] In contrast, most patients with advanced non-seminoma needed post-chemotherapy RPLND.[78,79] In Japan, experienced urologists take part in both chemotherapy and surgery and also carry out post-treatment follow up. The recent improvement of treatment outcome, especially that of patients with poor prognosis, is partly attributable to consistent management from chemotherapy to surgery by experienced urologists. Further centralization of hospital referral is needed in Japan, a country with a low incidence of germ cell tumor.

Conclusion

Development of the IGCCCG classification system makes it easy to compare trial results and to select risk-adapted management depending on an accurate estimation of each patient's individual prognosis. Currently, the first-line chemotherapy with BEP remains the standard management of metastatic testicular cancer. Three cycles of BEP for good-prognosis patients and four cycles of BEP for intermediate- and poor-prognosis patients are the standard first-line chemotherapy. To achieve an optimal outcome, BEP should be given without dose reduction at 3-week intervals to the extent possible. This is possible for most Japanese patients with appropriate use of G-CSF. Evidence from RCT suggests that four cycles of EP for good-risk patients and four cycles of VIP for intermediate- or poor-risk patients is preferable to BEP to avoid bleomycin toxicity. Although no universal prognostic criteria have been defined for the recurrent or refractory disease, the risk-adapted approach may clarify the role of HDCT in the second-line setting. Several investigations reported improvement of treatment outcomes including those from Japan. Among the multiple factors responsible, centralization of hospital referral, especially for advanced cases, may contribute to this progress. Persistent efforts toward more centralization and progress in clinical investigation are needed to increase the cure rate for patients with poor prognosis or relapsed disease.

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