Cisplatin and Ifosfamide with Either Vinblastine or Etoposide as Salvage Therapy for Refractory or Relapsing Germ Cell Tumor Patients

The Institut Gustave Roussy Experience

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BACKGROUND. Approximately 30% of patients with metastatic germ cell tumors require salvage chemotherapy for recurrent or refractory disease after first-line treatment. The optimal salvage chemotherapy regimen remains to be determined.
METHODS. Fifty-four patients with metastatic germ cell tumors who failed to be cured with first-line therapy, were treated with a salvage VIP/VeIP regimen including cisplatin (20 mg/m^2/d d1 to d5), ifosfamide (1.2 gm/m^2/d d1 to d5), and either etoposide (75 mg/m^2/d d1 to d5) or vinblastine (0.11 mg/kg/d d1 and d2) for 5 consecutive days every 3 weeks.
RESULTS. A complete remission was observed in 24 patients (44%) at completion of VIP/VeIP chemotherapy. In 17 patients (31%), complete remission was reached with chemotherapy alone, whereas four (7%) were rendered tumor-free by resection of the residual inactive tumor. Three patients (6%) became tumor-free by resection of the residual carcinoma. Ten other patients (19%) achieved a partial response, with normalization of serum tumor markers. Eleven of those thirty-four patients additionally received high-dose chemotherapy with hematopoietic stem cell support as consolidation treatment. Twenty patients (37%) were judged to be treatment failures because of either incomplete response (3 patients) or progression of disease (17). Myelotoxicity was severe, but no toxicity deaths were noted. After a median follow-up of 30 months, 23 patients (43%) are alive, 16 of whom (30%) are without evidence of progression of disease. Among patients who received high-dose chemotherapy, the relapse-free survival was 63% compared with 35% for patients who did not receive this consolidation treatment.
CONCLUSIONS. Currently available salvage chemotherapy with ifosfamide and cisplatin is predicted to cure approximately 30% of the patients who have failed first-line treatment. Whether high-dose chemotherapy with hematopoietic stem cell support after salvage VIP/VeIP could improve these modest results remains to be confirmed in a randomized study. ***Cancer* 1996; 77:1193–7.**
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The results of treatment for germ cell tumors (GCT) have been dramatically improved with cisplatin-containing chemotherapy. Treatment with bleomycin, etoposide, and cisplatin—the so-called BEP regimen—and the surgical removal of residual masses is the standard treatment for disseminated disease.[1] According to prognostic models and classifications, patients can be allocated to either good-risk or poor-risk groups.[2] Three cycles of BEP in good-risk patients and four cycles of BEP in poor-

risk patients provide 80–100% and 50–70% complete remission rates, respectively.[1] However, 10% of the patients in complete remission relapse. Therefore, about 30% of patients with GCT will require a salvage chemotherapy for refractory or recurrent disease.

During the past 15 years, only two drugs, etoposide and ifosfamide, have demonstrated response rates greater than 20% as single agents in the salvage setting.[3,4] The remarkable efficacy of etoposide rapidly led to its successful evaluation in first-line treatment.[5] Early clinical trials with ifosfamide in heavily pretreated patients suggested definite activity and provided the basis for further evaluation.[6] The first experience with ifosfamide, cisplatin, and etoposide or vinblastine (VIP or VeIP) in the salvage setting was developed by Loehrer et al[7] and provided encouraging results. We analyze in this report the Institut Gustave Roussy experience with VIP/VeIP in 54 patients with refractory or recurrent GCT.

PATIENTS AND METHODS

Initial Patient Characteristics

Between January, 1989, and December, 1993, 54 consecutive, previously treated patients with refractory or recurrent GCT received an ifosfamide- and cisplatin-based salvage chemotherapy regimen at the Institut Gustave Roussy. All patients were male. The median age at diagnosis was 27 years. Forty-five patients (83%) had testicular primary tumors. Forty-three patients (80%) had nonseminomatous GCT. Five patients with pure seminoma and elevated serum tumor markers were considered as having nonseminomatous GCT. Five patients with pure seminoma and negative markers were either metastatic at diagnosis (2 patients) or had failed to be cured by initial radiotherapy (3 patients). Twenty-one patients (39%) had an advanced disease according to the Indiana classification.[8] All but two patients received platinum-based chemotherapy according to different protocols as first-line treatment: BEP or EP (etoposide + cisplatin with or without bleomycin; 22 patients), VAB-6 (vinblastine + actinomycin-D + bleomycin + cisplatin + cyclophosphamide; 9 patients), $CISCA_{II}/VB_{IV}$ (cisplatin + cyclophosphamide + doxorubicin/vinblastine + bleomycin; 7 patients), PVB (cisplatin + vinblastine + bleomycin; 3 patients), PVeBV (double dose cisplatin + vinblastine + bleomycin + etoposide; 3 patients), or EC (etoposide + carboplatin; 8 patients). Responses to initial treatment were defined as follow: complete remission (CR): 24 patients; partial response with normal markers (PRMq−): 12; incomplete response (IR): 18. Among the 24 complete responders, 11 had achieved CR to chemotherapy alone (cCR), eight patients to chemotherapy + surgical resection of fibrosis and/or necrosis and/or mature or immature teratoma (pCR), and five patients to chemotherapy + surgical resection of residual active carcinoma (sCR).

Treatment Plan

Pretreatment evaluation at salvage consisted of physical examination, urinalysis, complete blood count, serum creatinine and serum electrolytes, liver enzymes, human chorionic gonadotrophin (hCG), α-fetoprotein (AFP), lactate dehydrogenase (LDH), and thoracoabdominal CT scan. Refractory disease was defined as progressive disease during previous cisplatin-based chemotherapy or within 1 month after the last cycle of treatment.[9] The VIP regimen was administrated daily for 5 consecutive days at the following dosages: cisplatin 20 mg/m^2/d with hyperhydration, ifosfamide 1200 mg/m^2/d with mesna dose-continuous infusion, and etoposide 75 mg/m^2/d. The dosages and schedule for cisplatin and ifosfamide administration were identical for the VeIP regimen, but vinblastine was administered instead of etoposide at a dosage of 0.11 mg/kg/d days 1 and 2 of each cycle. Courses were repeated every 21 days. If severe myelosuppression was present at day 22, daily blood counts were done. The subsequent cycle was withheld until granulocyte count was greater than 500/μl and thrombocyte count was greater than 100,000/μl. CT scans were repeated every two cycles or when progressive disease was suspected. Resection of the residual masses, when indicated, was performed 4–6 weeks following the last course of chemotherapy. Several patients received as consolidation treatment high-dose chemotherapy (HDCT) with etoposide, cyclophosphamide, and cisplatin or carboplatin, followed by hematopoietic stem cell support (HSCS).

Patients with CR or PRMq− status at the end of treatment entered a follow-up program of monthly repetition of tumor marker measurements and chest X-ray for 1 year, then once every 3 months. CT scans were repeated every 3 months for the first year. Survival duration was measured from the date of diagnosis until death or last follow-up examination. Response duration was measured from the end of the treatment until relapse or last follow-up examination.

RESULTS

Patient Characteristics

Patient characteristics at the onset of salvage treatment with VIP/VeIP are described in Table 1. Twenty-three patients (43%) had moderate or advanced disease according to the Indiana classification. Forty-four patients (81%) had not received prior salvage chemotherapy, whereas ten patients had been treated with a second-line chemotherapy regimen (9 patients) or a third-line chemotherapy regimen (1 patient) before entry in the present study. Twenty-one patients (39%) were judged to have refractory disease.

Clinical Responses

Twenty-five patients (46%) received the VIP regimen, and 29 patients, who had previously received etoposide, were

TABLE 1
Patient Characteristics at the Onset of VIP/VeIP Chemotherapy

Characteristics	No. (%)
Age (Y)	
Median	27
Range	15–55
Primary site	
Testis	45 (83)
Retroperitoneum	3 (6)
Mediastinum	5 (9)
Unknown	1 (2)
Histology	
Pure seminoma	10 (18)
Nonseminoma	43 (80)
Pure tumors	
Embryonal carcinoma	12
Yolk sac	1
Choriocarcinoma	2
Mature teratoma	3
Immature teratoma	1
Mixed tumors	24
Unknown	1 (2)
Metastatic sites	
Markers only	6 (11)
Retroperitoneum	30 (56)
Mediastinum	12 (22)
Lungs	19 (35)
Cervical lymph nodes	3 (6)
Liver	9 (17)
Bone	5 (9)
Brain	1 (2)
Others	7 (13)
Elevated serum tumor markers	
α Fetoprotein	25 (46)
Human chorionic gonadotropin	22 (41)
Lactic dehydrogenase	20 (48)[a]

VIP: etoposide, ifosfamide, and cisplatin; VeIP: vinblastine, ifosfamide, and cisplatin.
[a] Serum lactic dehydrogenase levels were not determined in 12 patients.

treated with the VeIP combination (Table 2). Among the 54 patients, 24 (44%) achieved a complete response after VIP (13 patients) or VeIP (11 patients) chemotherapy. In 17 patients (31%), CR was reached by chemotherapy alone, whereas four patients (7%) were rendered tumor free by the resection of residual inactive tumor. Three patients (6%) became tumor free with the complete resection of viable residual carcinoma. Ten other patients (19%) achieved a PRMq− status. Twenty patients (37%) were judged to be treatment failures because of either incomplete response (3 patients) or progressive disease (17 patients). Eleven patients (7 cCR and 4 PRMq−) additionally received HDCT with HSCS 4–6 weeks after the last cycle of VIP/VeIP chemotherapy as consolidation treatment. Of 24 patients with prior CR to first-line chemotherapy, 17 (71%) achieved a tumor-free status after VIP/VeIP, compared with 2 of 8 patients (25%) with prior PRMq− and 5 of 18 patients (28%) with incomplete response.

Outcome

Seven of the seventeen patients (41%) who attained a cCR status remain in continuous CR 3–67 months from the end of treatment, five of whom received HDCT with HSCS as consolidation treatment (Table 2). Ten patients relapsed: Three again achieved a CR with subsequent salvage therapy, which included $CISCA_{II}/VB_{IV}$, $CISCA_{II}/VB_{IV}$ followed by HDCT with HSCS, and VIP and HDCT with HSCS, respectively. Six patients died of disease progression, and one is still alive with disease. Among the 4 patients who obtained a pCR status, only 1 patient relapsed and is still alive with progressive disease. All three patients with sCR relapsed and ultimately died of progressive disease. Only 2 of the 10 patients with PRMq− status at the end of VIP/VeIP therapy remain in continuous CR 7 and 11 months after the end of treatment. These two patients received HDCT with HSCS as consolidation therapy. Two patients are alive with progressive disease, four died of progressive disease, and two died of toxicity during the intensive chemotherapy following the VIP/VeIP regimen. Sixteen of twenty patients who failed to respond to VIP/VeIP died of progressive disease, and 3 patients are alive with disease. Only 1 patient obtained a durable CR (34 months) after subsequent salvage therapy with $CISCA_{II}/VB_{IV}$ followed by HDCT and HSCS.

After a median follow-up period of 30 months, 23 patients (43%) are alive, 16 of whom (30%) are without evidence of progressive disease. The median relapse-free survival in responding patients was 6 months (range 1–67+ months). Among patients who received HDCT, the relapse-free survival was 63% compared with 35% among patients who did not receive this consolidation treatment. All 5 patients with mediastinal tumors died.

Toxicity

One hundred forty-nine cycles of chemotherapy were assessable for toxicity. Myelosuppression was severe. WHO Grade 3 neutropenia occurred in 15.4% and Grade 4 neutropenia in 67.8% of the cycles. Granulocytopenic fever requiring concurrent hospitalization was observed in 22 (15%) cycles. All of these episodes were managed with intravenous antibiotics. No septic shock was registered. Thrombocytopenia WHO Grade 3 was seen in 23% and Grade 4 in 31% of the cycles. No major bleeding episode occurred. Nonhematologous toxicity included peripheral neuropathy in 3 patients, a transient episode of encephalopathy in one patient, and a reversible elevation of serum creatinine in one patient. No toxicity deaths were observed. No difference between VIP and VeIP protocols could be detected in terms of toxicity. However, two pa-

TABLE 2
Response and Outcome after VID/VeIP Chemotherapy

Response to VIP/VeIP		Consolidation therapy with HDCT and HSCS	Subsequent relapse	Long term outcome			
				NED	Alive with disease	Dead of progression	Dead of toxicity
c CR	17	7	10 (2)	10 (5)	1 (0)	6 (2)	0
p CR	4	0	1	3	1	0	0
s CR	3	0	3	0	0	3	0
PRMq-	10	4	8 (0)	2 (2)	2 (0)	4 (0)	2 (2)
IR and PD	20	0		1	3	16	0
Total	54	11	22 (2)	16 (7)	7 (0)	29 (2)	2 (2)

VIP: etoposide, ifosfamide, and cisplatin; VeIP: vinblastine, ifosfamide, and cisplatin. HDCT: high dose chemotherapy; HSCS: hematologic stem cell support; NED: no evidence of disease; cCR: clincal complete response; pCR: pathologic complete response; sCR: surgical complete response; PRMq-: partial response with normal markers; IR: incomplete response; PD: progressive disease.
Numbers in brackets indicate patients who underwent HDCT with HSCS as consolidation therapy.

tients with PRMq− status after VIP/VeIP died of toxicity during the HDCT + HSCS procedure.

DISCUSSION

Immediately when cisplatin was introduced in chemotherapy protocols of GCT, a 20–40% failure rate was observed. These patients experiencing treatment failure were submitted to different salvage regimens, which differed between 1978 and 1990. The first salvage regimen after failure on the PVB protocol was the two-drug combination of etoposide and cisplatin.[10,11] The favorable prognostic impact of response to first-line therapy on the outcome of salvage treatment was highlighted.[11] After the demonstration of activity of ifosfamide as a single agent in pretreated GCT patients,[4,6] the results of the three-drug combination VIP were reported by Loehrer et al in 1986.[12] The CR rate was 33%, and the long-term no evidence of disease (NED) rate was 15%. In four subsequent studies that included 152 patients with refractory or recurrent GCT who received VIP or VeIP as salvage therapy, the overall response rate ranged from 25% to 56%, and the survival rate did not exceed 23–42%.[7,13–16] The observed 44% complete response rate in this study is entirely in agreement with these previous reports.

In analyzing the prognostic factors for outcome after VIP/VeIP chemotherapy, the response to first-line treatment was the most important predictor of success of salvage therapy in all studies.[7,12–14] We previously reported the prognostic factors of response to salvage chemotherapy in two successive analyses.[17,18] In the first report, the significant predictors were response to first-line therapy and the tumor marker levels.[17] In the second analysis, including the clinical data from 203 patients treated in three institutions, four independent adverse prognostic factors were identified: an incomplete response to first-line therapy, extragonadal origin of the tumor, presence of lung metastases, and elevated serum tumor marker levels.[18] In poor-risk patients, conventional VIP/VeIP salvage chemotherapy does not offer a meaningful chance for survival, and other approaches should be considered.

Looking for an improvement in the efficacy of salvage chemotherapy, we treated at the Institut Gustave Roussy 21 patients with double-dose cisplatin in combination with ifosfamide and etoposide.[19] The 20% long-term complete response rate was not different from that observed with standard doses, and toxicity was more profound. This approach was therefore discontinued. Another way to increase the dose intensity might be the use of hematopoietic growth factors. A recent study using granulocyte-macrophage colony-stimulating factor as an adjunct to VIP/VeIP chemotherapy suggested its limited clinical impact in reducing neutropenia and infection during treatment.[20]

Among new therapeutic strategies, the use of drugs not incorporated in the first-line regimen is attractive. Levi et al[21] reported interesting results with a three-drug combination of methotrexate, dactinomycin, and etoposide after failure of PVB. The long-term NED rate was 29%, suggesting that a completely noncross-resistant drug regimen excluding cisplatin might be an alternative with equivalent efficacy. However, this protocol became obsolete when etoposide was introduced in the first-line treatment. More recently, investigators at the Memorial Sloan Kettering Cancer Center reported the first experience with paclitaxel in patients with previously treated GCT.[22] Among 31 patients, 8 (26%) achieved a partial or complete response. These results suggest that paclitaxel is the first drug capable of inducing response rates greater than 20% since the introduction of etoposide and ifosfamide. Further studies will be necessary to address the question of its role in combination therapy.

Whether HDCT with HSCS is likely to improve the

results of salvage treatment remains a matter of debate. A number of trials with HDCT and HSCS were conducted during the late 1980s in this setting.[23] The status of the disease, i.e., refractory or not refractory, at the time of HDCT seems to be the most important predictive factor of long-term outcome. Patients with refractory disease are unlikely to enter into long-term CR. Among 153 patients with refractory disease reported in the literature, 22 (14%) attained long-term CR status. Conversely, 41 of 118 patients (35%) with nonrefractory disease achieved a sustained CR.[23] In the present series, only patients with nonrefractory disease received HDCT with HSCS. It is noteworthy that 7 of 11 patients (63%) who were treated with HDCT as consolidation treatment remain alive without evidence of disease compared with 8 of 23 patients (26%) who did not receive HDCT after complete or partial response to VIP/VeIP. However, these results are not conclusive; the indication for HDCT was left to the individual decision of physicians involved in the study. In a recent report from Indiana University, 17 of 25 patients (68%) remained free of disease after brief conventional-dose chemotherapy followed by two cycles of HDCT for initial relapse of GCT.[24] An international randomized trial is in progress to assess the role of HDCT with HSCS as consolidation after VIP/VeIP in the salvage treatment of responder patients.

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