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Pattern of Relapse after First Line Treatment of Advanced Stage Germ-Cell Tumors

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Abstract

Objectives: We performed a retrospective analysis of first relapses after cisplatin-based chemotherapy in patients with advanced germ-cell tumors, in order to better define the appropriate follow-up.

Methods: These patients were treated between 1986 and 1998 in two institutions. They were either followed after first-line chemotherapy at the same center or referred for relapse.

Results: Ninety-six patients relapsed (17.5% of the total number of patients treated in the same time period). Thirty-five (36.4%) patients had serum tumor marker levels (AFP, hCG and LDH) normal values. Sites of relapse were: abdominal in 47 (49%) patients, thoracic in 17 (17.7%), thoraco-abdominal in 15 (15.6%), and brain in 8 (8.3). Seven (7.3%) patients had elevated markers only, 1 (1%) had isolated supra-clavicular lymph node, 1 (1%) had bone metastasis only. Eighty-two patients (85%) relapsed during the first 18 months of follow-up. All patients with brain metastases at relapse and those who obtained sCR after chemotherapy relapsed within 8 months of follow-up. Sixteen patients underwent resection of growing teratoma.

Conclusions: These results allow to recommend extensive follow-up during the first two years after response to first line treatment. It includes marker level determination and whole body CT scan and less intensive work-up there after.

Keywords: Germ-cell tumors; Surveillance; Chemotherapy; Surgery

1. Introduction

Since the area of cisplatin, 80% of the patients with advanced germ cell tumor are cured with chemotherapy and surgical resection of residual masses. Standard treatment is 3 cycles of bleomycin, etoposide and cisplatin (BEP) for patients with good prognosis, and 4 cycles for patients with intermediate or poor prognosis, as defined by the International Germ Cell Consensus Classification Group (IGCCCG) [1] and the European germ cell Cancer Consensus Group [2].

Five to 10 percent of patients relapse after first-line chemotherapy. Half of the patients obtain a complete response after salvage treatment; 25% of these are alive at long term [3]. The standard salvage chemotherapy regimen is an association of vinblastine, ifosfamide and cisplatin (VeIP) and recently the association of taxol, ifosfamide and cisplatin [4]. Surgery is performed when residual disease is observed. In case of suspicion of growing masses with serum tumor marker levels within normal values, surgical resection is performed and confirmed possibly the diagnosis of growing teratoma.

Patients with low tumor burden and low serum tumor marker levels at relapse have a better outcome: early detection of relapse may enhance salvage treatment

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results. No specific study has addressed the question of optimal follow-up procedures. However recommendations have been made in this setting [2,5].

We have analyzed relapse characteristics retrospectively in two centers with the objective of defining practical principles of follow-up. All patients in both centers have had the same follow-up schedule.

2. Patients and methods

2.1. Study population

This is a retrospective study of first relapses in 96 patients obtaining complete response (CR) or marker-negative partial response (PR-) after first-line cisplatin-based chemotherapy. A total of 547 patients were treated during this period between 1986 and 1998 in the Centre Léon Bérard and Institut Gustave Roussy. They were either followed after first-line chemotherapy at the same center or referred for relapse.

2.2. Definition of response

Complete response (CR) is the disappearance of all metastatic lesions and the normalization of serum tumor marker levels during 4 weeks after the last cycle of chemotherapy. Clinical CR (cCR) is obtained by chemotherapy only, pathological CR (pCR) by the complete surgical exeresis of inactive (necrosis, fibrosis, and teratoma) residual disease and surgical CR (sCR) by the complete surgical exeresis of active (malignant components) residual disease. Partial response (PR) is a decrease of more than 50% of the sum of the greatest perpendicular diameter of all measurable lesions with the normalization of serum marker level (PR-). Progressive disease (PD) is a progression of more than 25% of the sum of the greatest perpendicular dimensions of any measurable lesion or the increase of the serum marker level.

Time of relapse was calculated from the end of treatment (chemotherapy or surgery) to the date of relapse.

2.3. Patient characteristics at diagnosis

Eighty-five (89%) patients had primary testis tumor, 5 (5%) had primary retroperitoneal and 5 had mediastinal tumors; one (1%) had other primary localization. Eighty-one (84.5%) patients had non-seminomatous germ-cell tumor, 12 (12.5%) had pure seminoma. In 3 patients with no histological examination because of bulky life-threatening disease, serum tumor marker levels were very high (AFP $>$ 10 000 ng/ml and or hCG $>$ 50 000UI/l) and clinical presentations were considered characteristic of non-seminomatous germ-cell cancer. Fifty-three (55%), 13 (13.5%) and 30 (31.5%) patients had good, intermediate and poor prognosis, respectively, as defined by the IGCCCG. Serum tumor marker levels and metastatic sites are listed in Table 1. All patients had initially CT scan of chest, abdomen and pelvis and MRI or CT scan of brain when they had a intermediate or poor prognosis. All patients received first-line cisplatin-based chemotherapy.

Sixty-eight patients obtained a complete response, 29 of whom had clinical complete response (cCR), 25 pathological complete response (pCR) and 14 surgical complete response (sCR); 28 patients obtained a partial response with normalization of serum tumor marker levels (PR-) after first-line treatment. The RPLND was not performed when size of residual masses was under 1cm or shrinkage more than 90% and when the residual masses are inextirpation.

Table 1
Patient characteristics at diagnosis

Number of patients	Number	%
Institut Gustave Roussy	49	51
Centre Léon Bérard	47	49
Primary tumor	**96**	**100**
Testis	85	89
Retroperitoneum	5	5
Mediastinum	5	5
Other site	1	1
Histology	**96**	**100**
Unknown	3	3
Pure seminoma	12	12.5
Non-seminomatous germ-cell tumor	81	84.5
Mature and/or immature teratoma primary site	34	35.4
IGCCCG prognosis	**96**	**100**
Good	53	55
Intermediate	13	13.5
Poor	30	31.5
Serum tumor marker level		
Normal hCG, AFP and LDH	16	17
hCG elevated	53	55
AFP elevated	65	68
LDH elevated	23	24
Metastatic sites		
Lombo-aortic lymph nodes	70	72.9
Lung	45	47
Mediastinal lymph nodes	19	20
Liver	13	13.5
No site	11	11.5
Supra-clavicular lymph nodes	7	7.5
Bone	3	3
Epidural involvement	1	1
Response after first-line cisplatin based chemotherapy	**96**	**100**
CCR	29	30.2
PCR	25	26
SCR	14	14.6
PR-	28	29.2

hCG: human chorionic gonadotropin, AFP: alphafetoprotein, LDH: lactate dehydrogenase, cCR: clinical complete response, sCR: surgical complete response, pCR: pathological complete response, PR-: partial response marker negative.

2.3.1. Follow-up

Patients were followed every 2 months during the first two years, then every 3 months during the third year, every 4 months during the fourth and every 6 months during the fifth year. They were followed annually thereafter. At each visit, they underwent physical examination, chest X-ray and serum marker level determination (human chorionic gonadotropin: hCG, alphafetoprotein: AFP, and lactate dehydrogenase: LDH). Thoraco-abdominal CT scan was performed every 6 months during the first two years, then annually. Central nervous system (CNS) imaging (CT scan or MRI) was performed when patients had neurological symptoms. Bone scan was indicated when patients had bone pains. At relapse, all patients underwent complete restaging work-up: physical examination, serum tumor marker level determination (AFP, hCG, LDH), MRI or CT scans of the brain and CT scan of chest, abdomen and pelvis.