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ORIGINAL REPORT

Chemotherapy As an Alternative to Radiotherapy in the Treatment of Stage IIA and IIB Testicular Seminoma: A Spanish Germ Cell Cancer Group Study

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ABSTRACT

Purpose
To assess the long-term efficacy and toxicity of front-line cisplatin-based chemotherapy in patients with stage IIA or IIB testicular seminoma.

Patients and Methods
Untreated patients with pure seminoma of the testis after orchiectomy, with clinical stage IIA or IIB, were considered eligible for this prospective observational study. Chemotherapy consisted of either four cycles of cisplatin and etoposide or three cycles of cisplatin, etoposide, and bleomycin.

Results
Between April 1994 and March 2003, 72 patients were entered onto the study at 26 participating centers. Eighteen patients had stage IIA disease, and 54 patients had stage IIB disease. Eighty-three percent of patients achieved complete response, and 17% achieved partial response with residual mass. After a median follow-up time of 71.5 months, six patients with stage IIB disease experienced relapse, and one of these patients died as a result of seminoma. Three patients experienced non–seminoma-related deaths (two died from a further esophageal carcinoma, and one died from an upper digestive hemorrhage). The estimated 5-year progression-free survival rates for patients with stage IIA or IIB disease were 100% and 87% (95% CI, 77.5% to 97%), respectively. Five-year progression-free and overall survival rates for the whole group were 90% (95% CI, 82% to 98%) and 95% (95% CI, 89% to 100%), respectively. Severe granulocytopenia and thrombocytopenia were observed in eight and two patients, respectively. Mild to moderate emesis, stomatitis, and diarrhea were the most common nonhematologic effects.

Conclusion
Chemotherapy is a highly effective and well-tolerated treatment for patients with stage IIA or IIB seminoma and represents an available alternative that could avoid some of the serious late effects associated with radiotherapy. Further studies focusing on long-term toxicities of different treatment modalities are needed.

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INTRODUCTION

Testicular seminoma affects mainly young men in the third and fourth decades of their lives. Most patients have stage I disease on diagnosis (disease confined to testis) and have an excellent prognosis by management with orchidectomy followed by surveillance, radiotherapy, or carboplatin.[1-3] Nevertheless, a small percentage of the patients will experience relapse during the follow-up period. For these patients and those who are diagnosed with more advanced disease, testicular seminoma is characterized by a tendency to spread primarily to lymph nodes and later hematogenously to the lung and other viscera. Given the exquisite sensitivity of seminoma to radiotherapy, this modality has long been considered the standard treatment for stage IIA and IIB seminoma. Radiotherapy, using different doses and target volumes, produces excellent results in these patients, with long-term relapse-free rates of greater than 85%.[4-8]

In patients with more advanced stages and in postradiotherapy relapses, cisplatin-based chemotherapy has demonstrated high activity, leading to high cure rates.[9-13] Its efficacy seems to be greater than that of radiotherapy in bulky stage II disease.[4,8] Therefore, cisplatin-based chemotherapy is now being widely used as a standard treatment for advanced seminoma stages.

Consequently, the majority of patients, even those with advanced metastatic disease, are cured now by applying available therapies. However, several recent series showed that an increased risk of development of secondary malignancies, often arising in the previous irradiation ports, exists in long-term survivors after radiotherapy for stage I or II seminoma.[14-17] Concern about this infrequent but extremely serious late effect has led to investigation of new alternatives for the management of these patients.

The Spanish Germ Cell Cancer Group launched a prospective protocol of treatment with frontline cisplatin-based chemotherapy as an alternative to radiotherapy in stage IIA and IIB testicular seminoma. The purpose of the present study was to assess the long-term results and toxicity of this treatment modality in a large population of patients treated in a wide multicenter setting.

PATIENTS AND METHODS

Patient Selection

Patients with a histologic diagnosis of pure seminoma of the testis and clinical stage IIA (retroperitoneal lymph node metastases < 2 cm) or IIB (retroperitoneal lymph node metastases of 2 to 5 cm) disease were included in the study. Results concerning 34 of these patients were previously reported within a wider series of patients with stages II to IV seminoma,[11] and their data are reviewed here with an updated follow-up. A central review of pathology was not performed in this study.

Patients had undergone prior inguinal orchidectomy. Staging procedures consisted of clinical examination; computed tomography scan of chest, abdomen, and pelvis; pre- and postoperative measurement of serum α-fetoprotein, β-human chorionic gonadotropin, and lactate dehydrogenase; and ultrasonography of the contralateral testis. Patients were required to have stage IIA or IIB disease either at diagnosis or as a relapse of a previous stage I seminoma, no previous treatment with radiotherapy or chemotherapy, and normal α-fetoprotein levels before and after orchidectomy. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 to 2, normal baseline hematologic parameters, and creatinine clearance of ≥ 60 mL/min. Patients with history of prior malignant disease and patients with significant cardiac or hepatic disease were not eligible for this study. The study was approved by the institutional review board of the coordinator center, acting as a central institutional review board. All patients gave informed consent according to the recommendations of the participating institutions.

Treatment

Primary cisplatin-based chemotherapy was administered. The recommended regimen consisted of four cycles of cisplatin 25 mg/m^2/d and etoposide 100 mg/m^2/d for 4 days (E400P)[11] or, alternatively, three cycles of cisplatin 20 mg/m^2/d and etoposide 100 mg/m^2/d for 5 days with weekly bleomycin 30 mg (BE500P). Cycles were administered every 3 weeks. Adequate hydration and antiemetic prophylaxis with dexamethasone and 5-hydroxytryptamine-3 antagonists were administered. Cycles were not started unless the granulocyte count was more than 1,000/mL and platelets were more than 100,000/μL. Prophylactic use of growth factors was not routinely recommended. However, if febrile neutropenia or granulocytopenia causing delay in the administration of the cycle was present, prophylactic granulocyte colony-stimulating factor over 10 days was administered in subsequent cycles. Surgical resection of postchemotherapy residual masses was usually performed when their size was larger than 3 cm or at the investigators' discretion.

Outcome Evaluation and Statistical Analysis

This study was designed as an observational study. Twenty-six centers participated in the study. Patients were registered at the start of treatment, and their information was recorded prospectively. The primary objectives of the study were to determine the progression-free survival and overall survival in a large population of patients with early stage II seminoma treated with cisplatin-based chemotherapy, with long-term follow-up. Secondary objectives were to assess response and toxicity of this treatment. National Cancer Institute Common Toxicity Criteria were used to analyze toxicity. The initially scheduled recruitment period was 5 years, with an expected approximate inclusion rate of 15 patients per year. However, as a result of a slower rate of inclusion, this period was prolonged twice for additional periods of 2 years, resulting in a total recruitment time of 9 years. Treatment failure was continuously monitored over the study period, and early termination of the study was planned if the relapse rate was greater than 15%, which was considered unacceptable.

Response was determined by computed tomography scan, tumor marker assay, and histopathology findings at postchemotherapy surgery. Progression-free survival was defined as the time from the start of chemotherapy to the date of tumor relapse or progression. Overall survival was defined as the time from the start of chemotherapy to the date of death from any cause. Actuarial survival curves were calculated using the Kaplan-Meier method. The 5-year survival rate and its 95% CI were calculated using actuarial nonparametric method.

RESULTS

Patient Characteristics

Between April 1994 and March 2003, 72 patients, who represented all of the patients treated at each of the 26 participating centers who were eligible and consented to participate, were enrolled onto the study. Median age was 32 years (range, 23 to 66 years). All patients underwent prior inguinal orchiectomy, and all presented with classical seminoma histology. Eighteen patients had stage IIA disease, and 54 had stage IIB disease. Thirteen of 72 patients had experienced a relapse of previous stage I disease on surveillance. In eight patients, prechemotherapy β-human chorionic gonadotropin serum levels were increased. The chemotherapy schedule administered consisted of E400P in 60 patients and BE500P in 12 patients. Nine patients received a total of three cycles, 60 patients received four cycles, and three patients received more than four cycles. Main patient characteristics are listed in Table 1. One patient with concomitant schizophrenia was lost to follow-up after chemotherapy. The median follow-up duration of the series was 71.5 months.

Table 1. Patient Characteristics

Characteristic	No. of Patients (N = 72)	%
Age, years		
Median	32	
Range	23-66	
Stage		
IIA	18	25
IIB	54	75
Disease at start of treatment		
Metastatic on diagnosis	59	82
Relapse of stage I on surveillance	13	18
Elevated prechemotherapy BHCG serum levels	8	11
Median elevated value, U/L	265	
Range, U/L	10-1,645	
Chemotherapy regimen administered		
Cisplatin and etoposide	60	83
Cisplatin, etoposide, and bleomycin	12	17

Abbreviation: BHCG, β-human chorionic gonadotropin.

Response and Survival

There were 60 (83%) complete responses with chemotherapy alone and 12 (17%) partial responses with residual mass and normal markers. No treatment failures to first-line chemotherapy were documented. In one patient, the residual mass was larger than 3 cm; in three patients, it was between 2 and 3 cm; and in eight patients, it was ≤ 2 cm. Two patients underwent resection of residual masses. Histologic findings of necrosis and fibrosis were found in both patients. No additional treatment was administered to any patient.

After treatment, no patient with stage IIA seminoma but six patients with stage IIB seminoma experienced disease relapse. In these six patients, who had been treated in five different centers, the median time to relapse was 11.6 months (range, 5 to 35 months). One of the patients who experienced relapse had required a dose reduction from the original E400P regimen as a result of comorbidity, whereas the remaining five patients received full doses without dose reductions or significant delays. Relapses were seen in the retroperitoneum only in four patients and in the retroperitoneum, lung, and mediastinum in two patients. Initial chemotherapy had been E400P in all patients. Two patients were treated effectively with salvage second-line chemotherapy, and one additional patient was treated successfully with chemotherapy and radiotherapy. The other three patients experienced a further relapse. One of these patients was treated successfully with salvage surgery and radiotherapy, and another patient was treated successfully with chemotherapy; the third patient had progressive disease after radiotherapy and chemotherapy and died.

Three patients experienced non–seminoma-related deaths during the follow-up. Two patients, one with stage IIA and one with stage IIB disease, developed an esophageal squamous cell carcinoma 4 and 2 years after seminoma treatment. The third patient, who had stage II disease, died as a consequence of an upper digestive hemorrhage 4 years after salvage chemotherapy for a relapse after E400P treatment. In these three patients, there was no evidence of seminoma at the time of death.

The estimated 5-year progression-free survival rates for patients with stage IIA and IIB disease were 100% and 87% (95% CI, 77.5% to 97%; Fig 1), respectively. Five-year progression-free and overall survival rates for the whole group were 90% (95% CI, 82% to 98%) and 95% (95% CI, 89% to 100%), respectively (Fig 2).

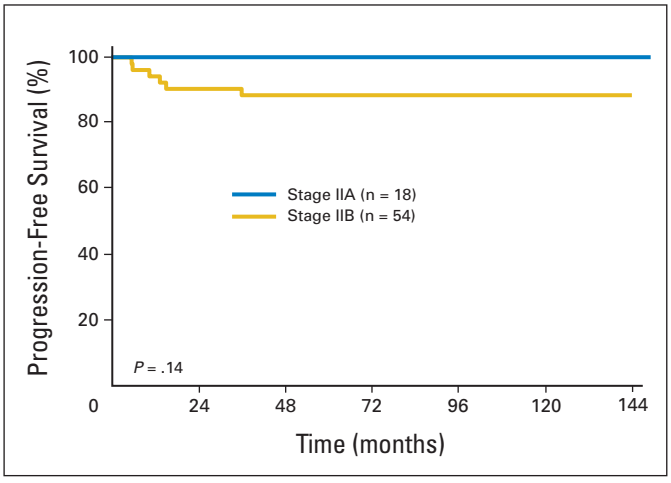

Fig 1. Progression-free survival curve for patients with stage IIA and IIB testicular seminoma treated with cisplatin-based chemotherapy.

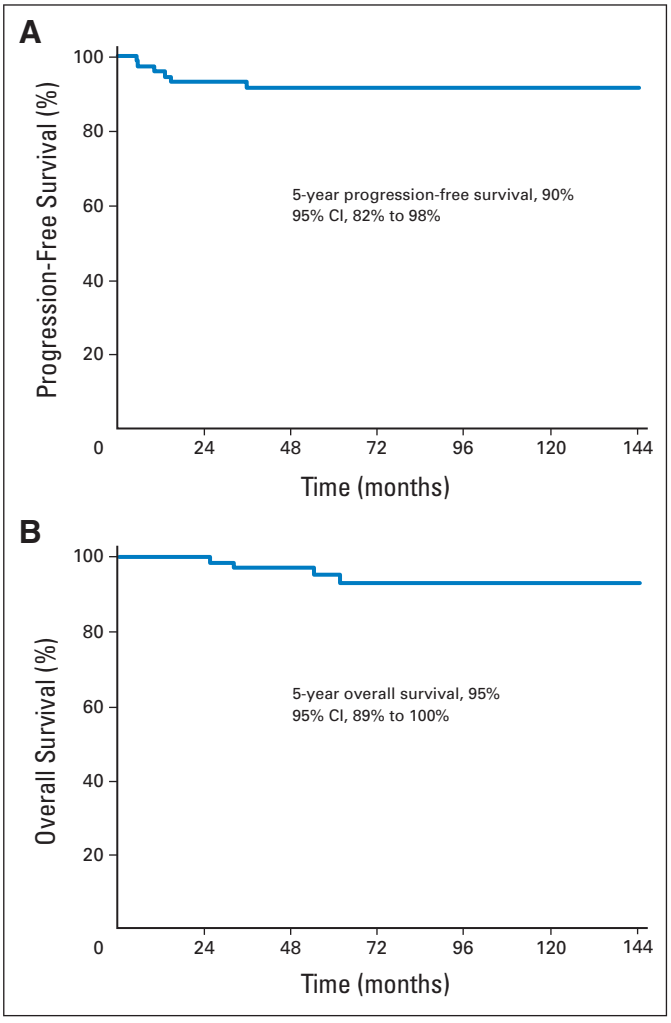

Fig 2. Survival curves for patients with stage IIA and IIB testicular seminoma treated with cisplatin-based chemotherapy. (A) Progression-free survival. (B) Overall survival.

Toxicity

Severe toxicities were uncommon and primarily hematologic. There were no toxic deaths. Table 2 lists the maximum grade of common toxicities observed in each patient. Grade 3 or 4 granulocytopenia was seen in nine patients, and eight of these patients experienced at least one episode of febrile neutropenia. Grade 3 thrombocytopenia occurred in two patients. One patient experienced grade 3 anemia. Nonhematologic toxicity was, in general, of mild to moderate intensity. Emesis, stomatitis, and diarrhea were the most commonly reported adverse effects. One patient treated with E400P experienced reversible grade 3 pneumonitis. Grade 2 neurotoxicity was observed in four patients, and grade 1 ototoxicity occurred in two patients. Alopecia was universal. As yet, after a median follow-up time of close to 6 years, no significant late toxicity has been reported.

DISCUSSION

Over the last decade, several studies have demonstrated that cisplatin-based chemotherapy yields high cure rates in patients with bulky

Table 2. Worst Toxicity by Patient

Toxicity	Grade 3 or 4		All Grades	
	No. of Patients	%	No. of Patients	%
Granulocytopenia	9	13	27	38
Thrombocytopenia	2	3	9	13
Anemia	1	2	4	6
Febrile neutropenia	8	11	8	11
Vomiting	6	8	33	46
Mucositis	1	2	6	8
Diarrhea	1	2	2	3
Pulmonary toxicity	1	2	1	2
Peripheral neuropathy	—	—	14	19
Rash	—	—	3	4
Ototoxicity	—	—	2	3
Alopecia	—	—	72	100

advanced seminoma and in patients who experience relapse after prior radiotherapy.[9-13] However, in early stage II disease, the availability of radiotherapy has precluded the development of chemotherapy, until now. Radiotherapy has long been used for the treatment of stage IIA and IIB seminoma, and numerous series have shown excellent results with this treatment. The radiation dose administered is usually between 25 and 40 Gy, and the treatment volume includes the para-aortic and the ipsilateral pelvic lymph nodes. The long-term relapse-free survival rate is usually between 85% and 90% and seems to be superior for stage IIA compared with stage IIB disease.[4-7] Nevertheless, the occurrence of relapses in a few patients, usually localized outside the radiation port, makes it necessary to have a long follow-up.[4] Furthermore, radiotherapy is usually an acceptably well-tolerated treatment.[5,18,19]

To our knowledge, this study is the first to assess the activity of cisplatin-based combination chemotherapy as frontline treatment in early stage II seminoma. The study was performed as an observational study that included all consecutive nonselected patients seen in a wide multicenter setting, and therefore, it provides reliable information on the effectiveness of this treatment in routine clinical practice. The results showed that chemotherapy is, as expected, highly active in the treatment of these patients, producing complete or partial response with negative tumor markers in 100% of the patients and providing excellent progression-free and overall survival figures that compare favorably with those classically reported after radiotherapy. In addition, chemotherapy was, in general, well tolerated. Severe toxicity was infrequent, and it was manageable and reversible.

The only previously reported experience of first-line chemotherapy treatment in early stage II seminoma used a single agent, carboplatin. Results were disappointing, showing a failure rate of 18%, with many patients requiring salvage treatment.[20] This finding is not surprising and is consistent with the results of two randomized studies that demonstrated that cisplatin-based combination chemotherapy is more active than carboplatin alone in advanced seminoma patients.[21,22] Another new approach that has been investigated is the combination of radiotherapy with a single course of carboplatin in stage IIA and IIB seminoma. In a series of 30 patients, the 5-year progression-free survival rate was 97%.[23] These results are promising when compared with radiotherapy alone, but additional investigation is needed, particularly regarding toxicity of the combination.

In our study, 60 patients received E400P, a modified regimen that included 400 mg/m^2 of etoposide per cycle, and 12 patients received the standard BE500P regimen with 500 mg/m^2 of etoposide per cycle. When the study was initiated in 1994, the E400P regimen was proposed with the intention of reducing the toxicity of chemotherapy by avoiding bleomycin and limiting the dose of etoposide because seminoma is a particularly sensitive subtype of germ cell tumor. Our first results in advanced seminoma showed promising activity and acceptable tolerance.[11] Lately, a large randomized phase III trial established the benefit, in terms of survival, of the BE500P regimen versus another regimen with lower doses of etoposide and bleomycin for germ cell tumors (BE360P).[24] Additionally, subsequent large studies have suggested that four cycles of E500P, with 500 mg/m^2 of etoposide, could be an alternative to three cycles of BE500P for good-risk germ cell tumors.[25,26] Therefore, nowadays, the recommended regimen of chemotherapy for stage IIA or IIB seminoma patients should be three cycles of BE500P or four cycles of E500P, instead of the E400P regimen. Furthermore, in our study, all relapses were observed after treatment with the E400P regimen, and none were observed after BE500P treatment. Although the number of patients treated with E400P was much larger, we cannot rule out a potential impact of lower dose etoposide on the relapse rate.

In a highly curable disease such as stage IIA and IIB testicular seminoma, prevention of long-term sequelae of treatment is a priority, especially when these sequelae might compromise the life of the patient. Recently, consistent data from several clinical series with long follow-up and studies based on cancer registries have revealed the existence of an increased incidence of secondary malignancies in long-term survivors of stage I and II seminoma treated with radiotherapy.[15,17,27-31] These tumors are usually located in radiotherapy fields and are commonly GI and genitourinary tract cancers, pancreatic cancer, and sarcoma.[29,30] The occurrence of this rare but severe late complication, in patients who are usually young and otherwise cured, resulted in the need to investigate new management alternatives that minimize this risk. In stage IIA and IIB seminoma, primary treatment with chemotherapy, as is done in more advanced stages, could be a reasonable option. The results of our study showed that this approach is feasible, yielding excellent efficacy results with an acceptable tolerance. Reduction in radiation volumes and doses[5] is another potential option that has been more extensively studied in stage I seminoma.[32,33] In the study of Zagars et al,[14] however, no differences were found in mortality as a result of secondary malignancies between patients receiving less than 25 Gy and those receiving more than 25 Gy. Therefore, further studies are needed to elucidate this issue.

In our study, two patients who had not received radiotherapy developed an esophageal cancer during the follow-up period. An increased risk of occurrence of this type of cancer in testicular cancer survivors was recently described, but it had been initially interpreted as possibly related to radiotherapy.[29,30] However, our observation suggests that the possible influence of other factors, such as chemotherapy, or the existence of shared risk factors cannot be ruled out and need further investigation. Indeed, a low but increased risk of development of acute myeloid leukemia associated with chemotherapy, especially when etoposide is administered in high cumulative doses, has been well established in testicular cancer survivors.[34,35] Furthermore, recent

large studies showed that survivors of testicular cancer have a consistently significant increased risk of secondary malignancies when compared with the general population.[29-31,35-37] A collaborative study that included a large population of 40,576 long-term testicular cancer survivors showed that this risk persisted for at least 35 years and may be higher for younger patients.[30] In this study, a significant risk of solid secondary tumors in patients treated with chemotherapy alone was observed, and this risk increased when radiotherapy and chemotherapy were combined. Although the number of analyzed patients treated with chemotherapy was low and the follow-up was short, this observation is particularly concerning and indicates that further studies are needed.

Also, the potential occurrence of late noncancer toxicities in survivors of testicular cancer treated with different modalities should be considered. In particular, cisplatin-based chemotherapy has been associated with some known late effects in these patients. Nephrotoxicity, ototoxicity, and neuropathy can persist to some degree in a small percentage of patients,[38] especially when a large number of cycles of cisplatin was administered. Infertility is not uncommon after chemotherapy, although many of these patients already had prior abnormalities in semen analysis. However, 50% to 80% of the patients recover normal sperm counts within 5 years from treatment.[39] Radiotherapy seemed to have a more deleterious effect on fertility than chemotherapy in testicular cancer patients in one study.[40] Of particular concern, several studies have recently reported an increased incidence of cardiovascular events in patients treated with cisplatin-based chemotherapy for germ cell tumors.[41,42] The development of metabolic syndrome,[43] a known cardiovascular risk factor, in some patients could contribute to this complication. Radiotherapy has also been associated with an increased risk of cardiac disease, mainly when prophylactic mediastinal irradiation had been administered.[14,44] Furthermore, a recent large study showed that mortality as a result of noncancer causes, such as infection, digestive diseases, and circulatory diseases, is slightly increased in testicular cancer survivors.[44] A recent study compared the long-term risks of second malignant neoplasms and cardiovascular diseases in a nationwide cohort of 2,707 testicular cancer survivors with a median follow-up time of 17 years.[31] In this study, the risk of second malignancy was increased by 2.6-fold after subdiaphragmatic radiotherapy and by 2.1-fold after chemotherapy. The risk of cardiovascular disease was increased by 1.7-fold after chemotherapy, whereas it was not significantly increased after subdiaphragmatic radiotherapy. All of these data concerning long-term toxicities indicate that studies to better determine their causes and to quantify specific risks of the treatments are critical to assess the advantages and inconveniences of different treatment modalities.

In conclusion, our study shows that chemotherapy is a highly effective and well-tolerated treatment for patients with stage IIA or IIB seminoma that yields excellent progression-free and overall survival rates. These results indicate that chemotherapy is an available alternative to radiotherapy in the treatment of these patients and could avoid some of the serious late effects associated with radiotherapy. Nevertheless, future studies focused on long-term toxicities of different treatment modalities are strongly recommended.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

