

ADJUVANT TREATMENT OF CLINICAL STAGE I SEMINOMA: IS A SINGLE COURSE OF CARBOPLATIN SUFFICIENT?

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ABSTRACT

Objectives. Adjuvant radiotherapy produces excellent disease-free rates in clinical Stage I seminoma. However, concern is growing about side effects and late hazards of this treatment. Carboplatin has been suggested to supplant radiotherapy. To date, there is little experience with this drug in the adjuvant treatment of seminoma. In particular, it is unclear whether one or two courses should be administered.

Methods. In a nonrandomized study, 125 patients with pure clinical Stage I seminoma were given adjuvant carboplatin treatment (400 mg/m²). Ninety-three patients received one course and 32 two courses. The median follow-up time was 48 months. To assess gonadal toxicity, serial measurements of follicle-stimulating hormone (FSH) levels were done. To assess myelotoxicity, platelet counts at 3 and 4 weeks after treatment were monitored.

Results. There were no relapses after two courses of carboplatin. After one course of carboplatin, eight relapses occurred (8.6%; 95% confidence interval [CI] 3.79% to 16.2%). All the relapses were located in the para-aortic region, and all the patients were rescued with cisplatin-based chemotherapy. The median time to recurrence was 16 months. The 5-year actuarial progression-free survival rate after one course was 91.1% (95% CI 85.25% to 97.01%). Younger patients (age groups: less than 30 years and 31 to 38 years) had relapses more frequently ($P = 0.038$) than those in the older age group (greater than 38 years). After 3 weeks, 32% of the patients had platelet counts below 150/nL. The median FSH level increased immediately after treatment, reaching a peak of 13.6 U/L. After 20 months, the median FSH level had returned to the normal range.

Conclusions. One adjuvant course of carboplatin was associated with low myelotoxicity and low gonadal toxicity; however, the recurrence rate was almost 9% and thus unsatisfactory. After two courses of carboplatin, no relapse was observed. Thus, the two-course regimen of carboplatin appears to be equivalent to radiotherapy, and because of its favorable toxicity profile, this regimen should be investigated in randomized trials. UROLOGY 55: 102–106, 2000. © 2000, Elsevier Science Inc.

In clinical Stage I seminoma, the traditional treatment consists of adjuvant radiotherapy.¹ Relapse rates range around 3% to 5%, and overall survival approaches 100%.^{2–4} Notwithstanding, dissatisfaction is increasing because of compro-

mises in quality of life during the application process of radiotherapy⁵ and because of growing concern about the late hazards of irradiation.⁶ Historically, surveillance was the first alternative intended to supplant radiotherapy,^{3,7–9} but the relapse rates of 15% to 20% were unacceptable. The early experience with carboplatin in the treatment of bulky seminoma^{10–12} fueled the enthusiasm for this drug because it was shown to be efficacious at a favorable rate of adverse effects. Consequently, pilot studies indicated that two courses of carboplatin appeared to be capable of eradicating micrometastatic disease. This regimen became even more appealing when Oliver *et al.*⁹ indicated that a single course of carboplatin might be sufficient for Stage I seminoma. To date, the single-course regimen of carboplatin has not been evaluated further.

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TABLE I. Patient characteristics

| | One Course Carboplatin (n = 93) | Two Courses Carboplatin (n = 32) | All Patients (n = 125) |
|--------------|---------------------------------|----------------------------------|------------------------|
| Age (yr) | | | |
| Median | 34 | 36 | 35 |
| Mean | 37.0 | 37.4 | 37.1 |
| Range | 23–73 | 22–61 | 22–73 |
| Follow-up | | | |
| Median (mo) | 48 | 45 | 48 |
| Range (yr) | 2–7* | 2–7 | 2–7 |
| 2 Years (n) | 13 (14) | 3 (9) | 16 (13) |
| ≥5 Years (n) | 34 (37) | 13 (41) | 47 (38) |

Numbers in parentheses are percentages.

* Except for 1 patient who was lost to follow-up after 2 weeks.

Thus, it was the purpose of the present trial to investigate the efficacy of the single-course regimen of carboplatin. In addition, we attempted to assess the gonadal toxicity and myelotoxicity by surrogate parameters.

MATERIAL AND METHODS

One hundred twenty-five patients with seminoma clinical Stage I from 18 institutions in Germany (see Appendix) were entered in a Phase II trial of adjuvant carboplatin treatment. Patient characteristics are presented in Table I. One patient who was infected with the human immunodeficiency virus but who was without the symptoms of acquired immunodeficiency syndrome was included. Patients having elevated serum levels of beta-human chorionic gonadotropin were included, but patients with elevated alpha-fetoprotein levels were not. None of the patients had elevated beta-human chorionic gonadotropin postoperatively. Staging consisted of computed tomography of the chest and abdomen and tumor marker analysis. Possible pathohistologic risk factors were not assessed in this study. The dosage of carboplatin was 400 mg/m². Ninety-three patients received one course of carboplatin. Because of personal decisions by the treating physicians, 32 patients received two courses of carboplatin 4 weeks apart. There was no randomization of patients to receive one or two cycles.

The follow-up evaluation consisted of computed tomography scans of the chest and abdomen, tumor marker assays, and a physical examination every 4 months during the first 2 years and every 6 months thereafter. The median time of follow-up was 48 months. One patient was lost to follow-up after 2 weeks. All the other patients had at least 2 years of observation. The patient lost to follow-up was counted as having a follow-up of 2 weeks with respect to the calculation of the actuarial relapse-free survival rate (Fig. 1).

To assess the effect of age on recurrence, the patient population was separated into three groups according to age, and the relapse rates in these groups were analyzed separately. To assess gonadal toxicity, serum levels of follicle-stimulating hormone (FSH) were examined at each visit during the first 3 years of follow-up. To assess myelotoxicity, white blood counts and platelet counts were performed weekly during the first 5 weeks after treatment. To increase compliance with the time schedule of the follow-up visits, each patient was given a "patient diary" that contained tear-sheets to be completed in duplicate after every visit. One duplicate was mailed to the

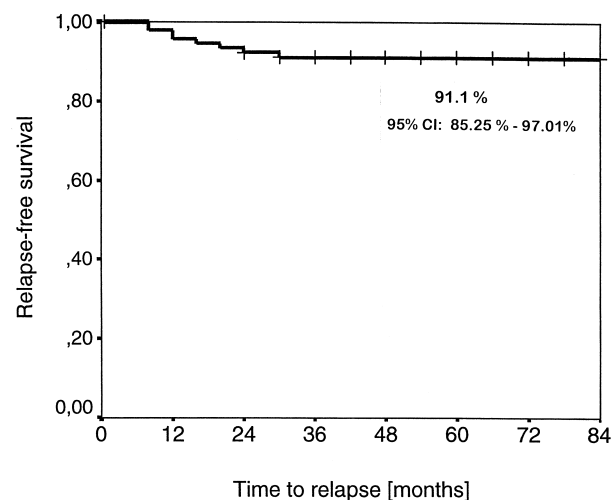


FIGURE 1. Actuarial relapse-free rate after one course of carboplatin (93 patients).

study center for evaluation, and the other was kept by the patient. Interim results of this study have been previously reported.¹³

Data management was accomplished by commercial personal computer program packages (dBase IV, MS Excel, and Scientific Package for Social Sciences [SPSS]). The rate of relapse-free survival was calculated according to Kaplan-Meier. The log-rank test was used to compare relapse rates among age groups and between types of treatment (one versus two courses). Ninety-five percent confidence intervals (CIs) were calculated for proportions and for the 5-year survival rates.¹⁴

RESULTS

Of the 93 patients receiving one cycle of carboplatin, 8 patients (8.6%) had relapses (95% CI 3.79% to 16.25%); all were located in the para-aortic region. The median time to recurrence was 16 months. The 5-year relapse-free survival rate (Fig. 1) was 91.1% (95% CI 85.25% to 97.01%). All the relapses were salvaged by three cycles of cisplatin-based combination chemotherapy, and all the patients were disease free at last follow-up. No relapse occurred among the 32 patients who received two cycles of carboplatin (95% CI 0% to 8.9%). Comparison of the two relapse rates by the log-rank test shows that the difference was not statistically significant ($P = 0.088$).

The overall survival and disease-specific survival rates after carboplatin (one and two courses) was 100%. The overall relapse-free survival rate was 93.4% (95% CI 89.02% to 97.84%). Recurrence was observed more frequently in the younger age groups (Table II). The difference was significant according to the log-rank test ($P = 0.0387$). The myelotoxicity after one course of carboplatin as measured by platelet count was low; no World Health Organization grade 2 toxicity was found. After 3 weeks, 32% of the 62 patients eligible for evaluation of myelotoxicity at this point had

TABLE II. Relapse rate according to age

| Age Groups (yr) | Patients (n) | Relapses (n) |
|-----------------|--------------|--------------|
| ≤30 | 35 | 5 (14.3) |
| 31–38 | 47 | 3 (6.4) |
| >38 | 43 | 0 (0) |

Numbers in parentheses are percentages.

Log-rank test for comparison of age groups; $P = 0.0387$.

thrombocytopenia, with platelet counts less than 150/nL. The median platelet count was 162/nL (mean 172; range 75 to 295). Four weeks after treatment, 14% of the 59 patients eligible had platelet counts less than 150/nL. The median count was 220/nL (mean 212; range 92 to 396). Gonadal toxicity as monitored by FSH levels is shown in Table III. Immediately after treatment, the median FSH level rose to 13.6 U/L and then slowly declined. Statistically, the mean values for FSH at all time points were higher than the corresponding median (Table III). This observation is probably explained by isolated patients with very high FSH levels. To circumvent the problem of confounding by isolated, very high FSH values, a second evaluation was done exclusively on those patients who had FSH levels that were not higher than 25 U/L at the outset. The curve of corrected FSH values (data not shown) was almost identical with the curve of uncorrected values.

Although not formally assessed, at least 6 patients fathered children after one course of carboplatin. Pregnancy onset ranged from 14 months after chemotherapy to 6 years. The patient with human immunodeficiency virus infection tolerated two courses of carboplatin without adverse events. One patient developed a contralateral testicular cancer 4 years after one course of carboplatin, and one other patient underwent excision of a squamous cell carcinoma of the nasal cavity 4 years after treatment.

COMMENT

EFFICACY

One course of adjuvant carboplatin treatment produced a relapse rate of almost 9%. The actuarial progression-free rate at 5 years was 91.1% (Fig. 1). From a clinical point of view, this result was clearly inferior to the optimistic results previously reported (Table IV),^{9,13,15} although, statistically, the confidence intervals overlap, and thus the difference is not truly significant. The high relapse rate after one adjuvant course is also in contrast to the reported results with two courses of carboplatin (Table V).^{16–18} Not surprisingly, it is also much higher than the radiotherapeutic recurrence rates of 2% to 5%.¹⁹

With respect to the one-course regimen of carboplatin, the data of the present investigation appear to be quite mature, since the number of patients is higher than in previous studies.^{9,15} Moreover, the median observation time in the present study was 48 months, as opposed to the 12 and 29 months, respectively, reported in these previous studies.

Underdosage of carboplatin could possibly be one reason for the unexpectedly high relapse rate in the present study. The 400 mg/m² dose, used in the present study, was the dosage used in the early trials with bulky seminoma to demonstrate the efficacy of carboplatin in this malignancy.^{10–12} As the activity of carboplatin is probably more dependent on the glomerular filtration rate than on the body surface area, Calvert *et al.*²⁰ proposed a dosage calculation model that used the area under the curve (AUC) when the carboplatin serum concentration is plotted against time. If carboplatin is used as a single agent, the target AUC should be 7 mg/mL per minute.²¹ On average, the doses calculated in this way are about 10% to 15% higher than those with the traditional dosage calculation. Thus, a possible underdosage cannot be disputed, but its impact on efficacy was probably not high. This conclusion is based on the small difference in dose found when the traditional dose and AUC-based dose were compared. The minor significance of the possible underdosing is also corroborated by the good efficacy of the traditional dose in metastatic seminoma^{11,12} and by the results of adjuvant trials with two courses of carboplatin (Table V), all of which used 400 mg/m².^{10,16–18} Accordingly, none of the 32 patients receiving two courses in the present study had a relapse.

One course of adjuvant carboplatin is not capable of eradicating micrometastases of seminoma sufficiently. After orchiectomy alone, the progression rate is approximately 15% to 20%.^{3,7–9} Abdominal micrometastases can be sterilized by radiotherapy and, most probably, also by two courses of carboplatin, resulting in a relapse rate of 2% to 4% if one of these adjuvant treatments is applied. As the relapse rate after the single course of treatment is about half of the rate of the surveillance regimen, it appears that at least some of the patients with micrometastatic disease might have benefited. Evidence for the cytostatic activity of even a single cycle of carboplatin is also provided by Yao *et al.*²² who treated small-volume metastases of seminoma with one course of carboplatin and additional radiotherapy. Restaging after the single course of treatment disclosed partial remissions in most cases.

The site of relapse was the para-aortic region in all cases in the present study. This pattern of relapse is identical with that found after surveillance.^{3,7,8} It is different from that observed after

TABLE III. FSH levels before and after one course of carboplatin

| | Before Treatment | After 5 wk | After 4 mo | After 8 mo | After 12 mo | After 16 mo | After 20 mo |
|--------------|------------------|------------|------------|------------|-------------|-------------|-------------|
| FSH (U/L) | | | | | | | |
| Median | 9.5 | 13.6 | 12.5 | 11.7 | 11.3 | 13 | 9.4 |
| Mean | 12.1 | 17.9 | 17.3 | 17.1 | 17.7 | 16.4 | 11.9 |
| Range | 1.1–45.3 | 3.2–73.8 | 4.3–71.0 | 3.8–70.9 | 1.3–91.5 | 5.0–38.2 | 2.8–24.6 |
| Patients (n) | 57 | 40 | 36 | 28 | 20 | 18 | 13 |

KEY: FSH = follicle-stimulating hormone.

TABLE IV. Efficacy of single course carboplatin—synopsis of reported series

| Authors | Year | Eligible Patients (n) | Median Follow-up (mo) | Relapses (n) | 95% CI |
|-----------------------------------|------|-----------------------|-----------------------|--------------|-----------|
| Oliver <i>et al.</i> ⁹ | 1994 | 25 | 29 | 0 | 0–11.3 |
| Mason <i>et al.</i> ¹⁵ | 1996 | 30 | 12 | 0 | 0–9.5 |
| This report | 1999 | 93 | 48 | 8 (8.6%) | 3.79–16.3 |

KEY: CI = confidence interval.

TABLE V. Efficacy of two courses of carboplatin—synopsis of reported series

| Authors | Year | Patients (n) | Median Follow-up (mo) | Relapses (n) | 95% CI |
|-------------------------------------|------|--------------|-----------------------|--------------|------------|
| Kratzik <i>et al.</i> ¹⁶ | 1993 | 39 | 20 | 1 (2.6) | 0.06–13.5 |
| Oliver <i>et al.</i> ⁹ | 1994 | 53 | 44 | 1 (2) | 0.048–10.1 |
| Krege <i>et al.</i> ¹⁷ | 1997 | 43 | 28 | 0 (0) | 0–6.7 |
| Nöst <i>et al.</i> ¹⁸ | 1998 | 29 | 52 | 0 (0) | 0–9.8 |
| This report | 1999 | 32 | 45 | 0 (0) | 0–8.9 |

KEY: CI = confidence interval.

Numbers in parentheses are percentages.

radiotherapy, because in-field relapses almost never occur.^{2,4}

Risk factors for progression were not formally addressed; however, relapse occurred more frequently among the younger patients. In one surveillance study, age younger than 34 years was associated with progression.²³ However, younger age might also be a chance finding, since two other surveillance studies failed to reproduce this observation,^{7,8} and, conversely, Oliver *et al.*⁹ found a trend toward older age in the patients with progression.

The median time to relapse was 16 months in the present study. Identical findings have been reported from the radiotherapeutic series^{2,3} and surveillance series.^{3,7,8}

TOXICITY

Late hazards (eg, hypertension²⁴ and second cancers^{3,25}) and quality-of-life data could not be assessed in the present investigation. Gonadal toxicity after carboplatin, however, appears to be rather low, as there was only a minor and transient eleva-

tion in FSH levels. The moderate impact on spermatogenesis was underscored by 6 patients fathering children during the follow-up period. Paternity shortly after carboplatin treatment had also been observed by Oliver *et al.*¹⁰ Additionally, a constant increase of semen quality beginning after 1 year of follow-up along with an only transient increase in FSH levels after two courses of carboplatin was reported by Reiter *et al.*²⁶ Although in the mouse and rat model, substantial damage to spermatogenesis had been observed,^{27,28} the review of clinical data clearly shows that carboplatin does not impose any permanent harm to the gonads when used in moderate doses.

In general, carboplatin's toxicity profile is more favorable than that of cisplatin; however, with respect to myelotoxicity, the opposite is true.¹² If carboplatin is used in high doses, severe myelodepression will result. In the present study, carboplatin was used in low doses and consequently, no World Health Organization grade 2 to 4 toxicity occurred. This result is in line with previous experience.¹⁷ Notwithstanding, the interpretation re-

quires caution, since the treatment consisted of one course only. After two courses, one might expect a somewhat higher degree of myelodepression.

The occurrence of two second cancers in this series was probably not etiologically related to carboplatin administration, since contralateral testicular tumors may occur at any time and nontesticular malignancies have been observed even before the diagnosis of a germ cell neoplasm.

CONCLUSIONS

The present nonrandomized study has shown that one adjuvant course of carboplatin is not capable of eradicating micrometastatic disease in a reliable manner. The relapse rate of almost 9% is unacceptable. However, if two courses of carboplatin are used, the recurrence rate appears to be acceptably low. Therefore, in light of the favorable toxicity pattern, this regimen seems rather promising and should be further evaluated in randomized trials.

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APPENDIX

The following is a list of the participating institutions (listed according to the number of patients, all located in Germany): Universitätsklinikum Benjamin Franklin, Berlin; Evangelisches Krankenhaus, Göttingen-Weende; Albertinen-Krankenhaus, Hamburg; Klinikum Villingen-Schwenningen; Urologische Praxis Dr. Brüggeboes, Baden-Baden; Universitätsklinikum Eppendorf, Hamburg; Humboldt Krankenhaus, Berlin; Allgemeines Krankenhaus St. Georg, Hamburg; Urologische Praxis Dr. Bloch, Hamburg; Urologische Praxis Dr. Schneider, Winsen/Luhe; Allgemeines Krankenhaus Barmbek, Hamburg; Evangelisches Krankenhaus Huysens-Stiftung, Essen; Franziskus-Krankenhaus, Berlin; Urologische Praxis Dr. Bünz, Hamburg; Krankenhaus Alfeld; Allgemeines Krankenhaus Altona, Hamburg; Stadt Krankenhaus, Cuxhaven; and Stadt Krankenhaus, Salzgitter.