Single agent carboplatin for CS IIA/B testicular seminoma. A phase II study of the German Testicular Cancer Study Group (GTCSG)


1 University/Medical School, Urology, Essen; 2 Wissenschaftlicher Service Pharma, Langenfeld; 3 Bundeswehrkrankenhaus, Urology, Hamburg; 4 University/Medical School, Urology, Muenster; 5 Albertinenkrankenhaus, Urology, Hamburg; 6 Standortische Kliniken, Urology, Kassel; 7 Klinikum der Stadt Schwenningen, Urology, Villingen/Schwenningen; 8 Kliniken Essen-Mitte-Hyssens-Stift, Urology, Essen; 9 University/Medical School, Medical Oncology, Halle; 10 University/Medical School, Medical Oncology, Marburg, Germany

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Background: The aim was to investigate the use of single agent carboplatin in patients with seminoma stage IIA/B.

Patients and methods: In a prospective phase II trial, single agent carboplatin at a dose of AUC 7 mg-C1 min/ml every 4 weeks for three cycles in stage IIA (n = 51) or four cycles in stage IIB (n = 57) was given to 108 patients with previously untreated seminoma stage IIA/B. Patients with residual masses of ≥3 cm were scheduled to receive secondary surgery.

Results: A complete response (CR) was achieved by 88/108 (81%) patients, 17/108 (16%) achieved a partial response (PR), two of 108 (2%) showed no change, and one patient progressed. In all patients with PR the residual disease was ≤3 cm; yet in two of 17 patients with PR, in two of two patients with NC and in one patient with disease progression residual tumor resection was performed demonstrating vital seminoma. Toxicity was acceptable with grades 3 and 4 myelosuppression, nausea and vomiting in less than 10% of patients each. After a median follow-up of 28 months (range 1–68 months) 14/108 (13%) patients relapsed, all after having achieved a CR. All relapses occurred in the retroperitoneum. One patient died from an unrelated cause. The overall failure rate was 19/108 patients (18%). The overall and disease specific survival was 99% and 100%, respectively.

Conclusions: Four cycles of single agent carboplatin AUC 7 do not safely eradicate retroperitoneal metastases in patients with stage IIA/B seminoma.

Key words: chemotherapy, carboplatin, testicular seminoma stage IIA/B
The protocol scheduled follow-up visits every 2 months during the first year and every 4 months during the second year, thereafter every 6 months for at least 3 years. Follow-up examinations included tumor markers β-HCG, AFP and lactate dehydrogenase (LDH). The AUC dosing was based on the calculated creatinine clearance instead of the measured EDTA-clearance, which is not routinely used in Germany. For calculation of the creatinine clearance any standard formula such as described by Cockroft et al. or Jeliffe et al. could be used, which have been shown to correlate well with the actual creatinine clearance [13].

Tumor extension was assessed by spiral computerized tomography of the thorax and the abdomen. Full blood counts were repeated 7 and 14 days after each cycle of chemotherapy and before the next one to define toxicity nadirs. Restaging was performed after two cycles of chemotherapy. In case of partial or complete response, upon restaging, the treatment schedule was completed. Otherwise the regimen had to be switched to cisplatin-based combination chemotherapy. For radiological residual disease with a maximum diameter <3 cm after completion of chemotherapy only follow-up was recommended.

The protocol scheduled follow-up visits every 2 months during the first year and every 4 months during the second year, thereafter every 6 months for at least 3 years. Follow-up examinations included tumor markers β-HCG, AFP and LDH, chest X-ray, computerized tomography or sonography of the abdomen and pelvis as well as sonography of the contralateral testis. The use of sonography instead of abdominal CT-scans during follow-up visits varied in individual patients at the decision of local investigators. Side-effects during chemotherapy were classified according to the WHO criteria.

Complete response (CR) was defined as the disappearance of all radiological evidence of tumor for a minimal duration of 4 weeks. Residual lesions with a maximum diameter ≤0.5 cm were also considered to represent partial remission. A partial response (PR) was defined as radiological residual disease of >1 cm, but a decrease of 50% or greater in the sum of the products of the perpendicular diameters of all lesions lasting for at least 4 weeks. Any increase in tumor size of less than 50% or an increase of no more than 25% was considered stable disease. Disease progression was defined as a greater than 25% increase in tumor size, the appearance of any new lesion or biochemical evidence of progressive disease.

The results of the study were as follows:

**patient characteristics**

From August 1995 until January 2001, a total of 108 patients at a median age of 38 years had been treated (range 20–65 years, Table 1); 51 patients had stage IIA and 57 had stage IIB disease. A biopsy of the contralateral testis was performed in 75 patients without demonstrating testicular intraepithelial neoplasia. Prior to orchidectomy an elevated β-HCG was found in 22 patients with a median value of 159 U/l (range 3–1743 U/l).

**treatment**

One patient with stage IIA refused further chemotherapy after the first cycle of carboplatin because of hematuria, although a causal relationship with the drug application was unlikely as no thrombocytopenia had been observed at that time. One patient with stage IIB discontinued chemotherapy after the third cycle because of grade II ototoxicity. Both patients underwent definitive radiotherapy. A further patient refused a fourth cycle of carboplatin due to personal reasons. In five patients impairment of renal function was observed resulting in dose modifications. In three other patients the administration of at least one cycle was delayed due to myelosuppression, noncompliance and a cerebrovascular event (one patient each).

**toxicities**

A summary of the maximal toxicities during chemotherapy according to the WHO classification is given in Table 2. The main toxicities were myelosuppression and gastrointestinal side-effects with leukocytopenia WHO grade 3 occurring in 4% of patients, thrombocytopenia WHO grade 3 and 4 in 6% and 2% of patients as well as nausea and vomiting grade 3 in 9% of patients, respectively. Other toxicities including nephrotoxicity, ototoxicity, infection or alopecia did not exceed WHO grade 2. One patient suffered from hematuria without a likely relationship to either his tumor or the administration of carboplatin.

**responses**

A complete response was seen in 88/108 (81%) patients, 17/108 (16%) patients had a partial response, two of 108 (2%) patients had no change and one patient had progressive disease despite...
carboplatin treatment (Table 3). All patients with PR had radiological residual disease <3 cm after completion of their treatment. Although not recommended by the protocol, two patients with residual lesions of 1 cm diameter were resected as well as both patients who had no change and the patient who progressed despite chemotherapy. In all five patients who underwent resections of their residual tumors the histology revealed vital seminoma. All five patients received adjuvant chemotherapy with two cycles of BEP and no patient relapsed.

relapse and survival
After a median follow-up of 28 months (range 1–68 months) 14/88 patients relapsed from CR for an overall relapse rate of 16%. Five additional patients who did not achieve a CR had vital seminoma at secondary surgery, resulting in an overall failure rate of 19/108 (18%) (Figure 1). Overall, eight of 51 (16%) stage IIA patients and six of 57 (11%) stage IIB patients relapsed. The median time to relapse was 6 months (range 2–27) overall; 5.5 months (range 2–27 months) for stage IIA patients and 6.5 months (range 5–9 months) for stage IIB patients. However, as all patients who failed carboplatin treatment could be effectively salvaged by second-line treatment, the disease specific survival was 100% and the overall survival was 99% (Figure 2).

All relapses occurred in the retroperitoneal lymph nodes in the region of the primary metastatic disease. Only one patient relapsed with an additional mediastinal mass (Table 4). One patient developed a recurrence of his seminoma 3 months after completion of carboplatin treatment and underwent resection of lymphnode metastases followed by two cycles of adjuvant chemotherapy with bleomycin, etoposide, cisplatin (BEP). After 8 months this patient developed a parailiacal mass, which was found to be related to a rectal carcinoma. This patient died from rectal cancer after 36 months. A second patient with a retroperitoneal relapse after 8 months underwent resection of retroperitoneal and lower mediastinal lymph nodes followed by four cycles of cisplatin, etoposide and ifosfamide. After a further 10 months this patient developed a second recurrence in the mediastinum and achieved a CR after high-dose chemotherapy and irradiation. In a third patient who had received a lymphadenectomy for his first retroperitoneal relapse after 5 months followed by three cycles of BEP, a second retroperitoneal relapse occurred after a further 16 months. He was treated with high-dose chemotherapy and has remained in continuous complete remission ever since.

Despite the fact that the protocol recommended chemotherapy in case of relapse, more than half of the relapsing patients underwent surgery as their first intervention. The exact reasons for this strategy varied. However, as all of the relapses developed within the primary lymph node metastases, some urologists may have suspected possible non-seminoma, teratoma or sarcoma histologies in these patients.

At the time of the first planned interim analysis, the overall failure rate of 19/108 (18%) (95% CI 11% to 26%) fulfilled the predefined criteria of early stopping and required the premature termination of the study according to the statistic plan.

discussion
In this prospective multicenter phase II trial single-agent carboplatin was investigated as an alternative treatment to radiotherapy in stage IIA/B seminoma with the following main

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Kaplan–Meier curve of relapse free survival and failure free survival (combination of failures during therapy and relapses).

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Kaplan–Meier curve of disease specific and overall survival.

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>WHO grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Anemia</td>
<td>49</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>26</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21</td>
</tr>
<tr>
<td>Creatinin</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>49</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5</td>
</tr>
<tr>
<td>Haematuria</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2.** Toxicity during chemotherapy with three or four cycles of carboplatin; highest degree of toxicity over all cycles

<table>
<thead>
<tr>
<th>Response</th>
<th>Total (n=108)</th>
<th>IIA (n=51)</th>
<th>IIB (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>88 (81%)</td>
<td>46 (90%)</td>
<td>42 (74%)</td>
</tr>
<tr>
<td>PR</td>
<td>17 (16%)</td>
<td>4 (8%)</td>
<td>13 (23%)</td>
</tr>
<tr>
<td>NC</td>
<td>2 (2%)</td>
<td>–</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>–</td>
</tr>
</tbody>
</table>

**Table 3.** Response rate after three to four cycles of carboplatin therapy
issues: first, to assess the acute toxicity profile and second, to determine the response, relapse and survival rates with this treatment. The background for this trial was the relatively high relapse rates with standard radiation treatment, especially in stage IIB patients [2], as well as concerns about acute and possible long-term toxicities such as secondary cancers [4, 16, 17]. The main reason to evaluate single-agent carboplatin in stage IIA/B seminoma at an empirical dose of AUC 7 was its high single-agent activity in stage I disease [5–8] and even in advanced seminoma, as well as its favourable toxicity profile [9–13].

The data from our study confirmed the low toxicity acute profile of carboplatin. Main side-effects were nausea in about half of the patients, mild to moderate emesis and myelosuppression. Whereas the frequency and severity of such gastrointestinal side-effects compare favourably with those reported after radiation treatment, the rate of myelosuppression appeared to be higher after single-agent carboplatin compared with after radiation treatment. The frequency of long-term toxicities and in particular the possible benefit of single-agent carboplatin in reducing the rate of secondary cancers will require more follow-up and cannot be assessed at the present time.

The other aim of this study, to establish an equally effective treatment alternative to radiotherapy with the use of single-agent carboplatin, could not be achieved. After a median follow-up of 28 months, carboplatin treatment failed to reliably eradicate even low volume metastases in 19/108 patients (18%). It is of particular note that there were no differences in the relapse rates between stages IIA and IIB and that all relapses occurred at the primary metastatic regions. Although better results might have been achieved if four cycles of carboplatin had been used also in stage IIA patients, these results indicate that single agent carboplatin is insufficient to eradicate even low volume metastatic seminoma deposits.

Chung et al. [18] compared the efficacy of radiotherapy and a combination chemotherapy with etoposide and cisplatin in patients with stage IIA/B seminoma. Seventeen per cent of patients treated with radiotherapy and only 6% of those treated with chemotherapy relapsed, but the 5- and 10-year cause-specific and overall survival was similar with 94% and 93% for both.

But despite a failure rate of 18% after single-agent carboplatin treatment in this trial, all patients were salvaged by cisplatin-based combination chemotherapy with or without surgery resulting in a disease-specific survival of 100% and an overall survival of 99% after a median follow-up of 28 months. Thus the salvage rates after carboplatin are similar to the ones in case of failure after radiation treatment of seminoma stage IIA/B [19]. Carboplatin pretreatment does not, therefore, seem to compromise cisplatin-based salvage treatment of such patients.

Treatment with single-agent carboplatin may have practical advantages in individual patients. Radiation treatment with 30 Gy or 36 Gy is usually administered in 15 and 18 fractions, respectively, and requires the use of a linear accelerator. In contrast, single-agent carboplatin can easily be administered as a short intravenous infusion on an outpatient basis at almost any experienced oncology unit. Therefore, for patients who do not live close to a major cancer center or in countries with limited access to radiation facilities, single-agent carboplatin might be a more feasible alternative to radiation treatment.

Cisplatin-based combination treatment is commonly considered to be the main alternative to radiation treatment in
advanced seminoma and has a higher anti-tumor activity than single-agent carboplatin [10, 11]. The UK Medical Research Council conducted a trial in advanced seminoma to compare single-agent carboplatin with a combination chemotherapy of etoposide and cisplatin. The progression-free survival rate at 3 years was 71% in patients who received carboplatin \((n = 64)\) and 81% in those allocated etoposide and cisplatin \((n = 66)\). The overall survival rates at 3 years were 84% and 89%. Although the trial was already closed after recruitment of 130 patients, it showed no statistically significant difference in the major survival end points. However, higher acute toxicities of cisplatin-based treatment compared with single-agent carboplatin could be demonstrated [12]. This was confirmed in a large randomized trial in Germany. Although the relapse rate in these patients treated with single-agent carboplatin was 21% compared with only 4% in patients treated with cisplatin, etoposide and ifosfamide (VIP), the overall survival with 87% and 95% was not significantly different. In contrast, grade 3 and 4 toxicities were substantially higher in the VIP-treated group (72%) compared with the group treated with single-agent carboplatin (8%) [13].

Yet another approach was pursued by Patterson et al. [20] who treated 30 patients with single-agent carboplatin 4–6 weeks prior to infradiaphragmatic radiotherapy and compared this treatment with the results in 80 patients who received radiotherapy alone. The 5-year relapse-free survival was 92% for the combination therapy and 85% for irradiation alone in stage IIA and 100% versus 70% in stage IIB patients \(<0.05\). Although these data suggest that single-agent carboplatin in combination with radiation treatment may be more effective than radiation treatment alone, the combination of radiation and chemotherapy might also increase acute and long-term toxicities such as the risk of secondary tumors.

In conclusion, the results of the present trial confirm that radiotherapy remains the standard treatment in seminoma stages IIA/B. Due to its superior efficacy, cisplatin-based combination chemotherapy is the major alternative to radiation treatment. However, for those patients in whom either treatment is not feasible, four cycles of single-agent carboplatin at an AUC of 7 represent yet another well tolerated and effective approach.

**references**

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**appendix**

This has been a multicenter study, the following are members of other participating clinics:

A. Heidenreich, Universitätsklinik Köln; M. Fallahi, Klinikum Barmen, Wuppertal; P. Kwasy, Städtische Kliniken Dortmund; G. Block, Kreiskrankenhaus Völklingen; St. Schmidt, Stadtkrankenhaus Cuxhaven; J. Lebentrau, Klinikum Ernst von Bergmann, Potsdam; M. Olszewski, Helius Klinikum Aue; S. Kloß, DRK-Krankenhaus Luckenwalde; A. Kraibich, Krankenhaus am Friedrichsain Berlin; T. Szaby, Husum; P. Marong, St. Katharinen-Krankenhaus Frankfurt; U. Rüther, Katharinenhospital Stuttgart; G. Lüdecke, Universitätsklinik Gießen; A. Bannowsky, Universitätsklinik Kiel; T. Övermöhle, St. Franziskus-Hospital Lohne; B. Haben, St. Antonius Hospital Eschweiler; G. Leibfried, Kreiskrankenhaus Hagold; M. Pechol, Universitätsklinik Greifswald; J. Rosenberg, Klinikum Meinigen; U. Niekerken, St. Elisabeth Krankenhaus Neuwied; A. Stammel, L. Schapiro, Wesel; K.U. Köhrmann, Theresienkrankenhaus Mannheim; D. Schittelpopp, Städtische Kliniken Magdeburg; T. Mügge, St. Bernward Krankenhaus Hildesheim; St. Presse, Städtisches Klinum Fulda; F.J. Marx, Krankenhaus Holweide, Köln; R. Anding, Kreiskrankenhaus Ludenscheid.