The long-term risks of adjuvant carboplatin treatment for stage I seminoma of the testis

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Background: The use of adjuvant carboplatin in the management of stage I seminoma of the testis has been limited by the lack of long-term data. In this study, we address this issue for the first time.

Patients and methods: Data on 199 patients treated with single-agent carboplatin for stage I seminoma of the testis were prospectively collected. Overall mortality, deaths from circulatory disease and the incidence of second cancers were compared with expected values derived from the UK general population.

Results: The median follow-up for the cohort was 9.0 years (range 0.1–20.1). There has been no excess in overall mortality (standardised mortality ratio (SMR) 0.89; 95% CI 0.36–1.83), death from circulatory diseases (SMR 1.44; 95% CI 0.39–3.69) or the incidence of second nontestis cancers (standardised incidence ratio 0.96; 95% CI 0.26–2.45) in this group of patients. These findings also applied to specific follow-up periods of >5 or 10 years. Specifically, neither haematological nor solid nontestis tumours occurred in excess. There was an increase in the long-term development of contralateral testis cancers.

Conclusions: This study addresses some of the concerns surrounding the long-term safety of single-agent carboplatin. It also helps in planning long-term follow-up for patients receiving this form of treatment.

Key words: adjuvant, carboplatin, mortality, testis cancer, second cancers, seminoma, stage I

introduction

Attempts have been made to reduce the proportion of patients who relapse with stage I seminomas. Radiotherapy has established itself as an adjuvant treatment, which significantly reduces the relapse rate [1–5]. Unfortunately, radiotherapy is associated with doubling in the risk of developing a second malignancy compared with the general population [6–10]. This risk only becomes apparent after 5 years and peaks between 10 and 20 years after treatment [7]. Radiotherapy is also associated with an increased risk of cardiovascular events in the long term [11, 12]. Indeed, patients treated with radiotherapy have a decreased survival compared with matched individuals from the general population [12].

For these reasons, alternatives have been sought. Single-agent carboplatin has been investigated in a randomised study and was shown to have a similar relapse rate and overall survival compared with radiotherapy in this setting [13]. Unfortunately, there are no long-term follow-up data for this form of treatment, and as combination chemotherapy for testis cancer is associated with increased mortality, cardiovascular disease and second cancers, there are justified concerns about the long-term side-effects associated with single-agent carboplatin [7, 9, 10, 14–18]. Consequently, the use of routine single-agent carboplatin has not been widely recommended [17]. In this study, we present the long-term risks of single-agent carboplatin treatment for stage I seminoma.

patients and methods

From 1986 to January 2007, patients were offered single-agent adjuvant carboplatin for stage I seminoma of the testis at our institution. Data on these patients were recorded in a prospective database. This regimen was offered to all patients as part of consecutive phase I/II/III studies [13, 19]. A number of individuals did not want to enter into these studies and were offered surveillance (n = 86) or adjuvant radiotherapy (n = 29) instead.

The dose of carboplatin given changed with time as area under curve became widely used to calculate the dose during this study (Table 1) [20]. During the first 5 years of this approach, two cycles of carboplatin were given (n = 28), after which only one cycle was given (n = 171). The reasons for this are the results of the initial studies which indicated that one cycle was as effective [19]. Patients were followed up according to our in-house protocol. This included three monthly outpatient appointments for the first 2 years, followed by four monthly outpatients until 5 years. Patients had tumour markers measured. Routine radiological investigations stopped at 2-year follow-up. After 5 years of follow-up, patients were seen on an annual basis. Outcome data for these patients were recorded. These included date and cause of death, the development of a second tumour and the development of a second testis cancer.

The outcome of the cohort was assessed in January 2007. Seven patients had been lost to follow-up (last contact 3–9 years ago). All these patients...
moved within the UK or emigrated (three to Europe, one to Asia and one to Australia).

cardiovascular and overall mortality
Observed deaths were compared with the expected numbers derived from age–sex–cause–specific rates for England and Wales in 1999, as published by the Office for National Statistics [22]. Standardised mortality ratios (SMRs) were calculated with exact 95% Poisson confidence intervals (CIs). Cerebrovascular disease and ischaemic heart disease were assessed separately, along with all-cause mortality.

incidence of second cancers
The observed occurrences of cancers subsequent to treatment with carboplatin were compared with the expected numbers derived from age–sex–period–specific rates for South East England from the Thames Cancer Registry. Time at risk was calculated from the start of treatment to the date of last follow-up, death or diagnosis of second cancer. Standardised incidence ratios (SIRs) were calculated with 95% CIs. Occurrences of testis cancer and haematological cancers were assessed separately. Subset analyses were carried out for patients with follow-up of >5 and 10 years.

results

patient characteristics
Overall, 199 patients with ongoing follow-up were identified from the database, with a total follow-up of 1841 person-years and median follow-up of 9.0 (range 0.1–20.1) years. Seventy-four per cent had a follow-up of >5 years, and 45% had >10 years of follow-up. The median age at the time of carboplatin treatment was 36 years (range 19–73), and the median age at the most recent follow-up was 45 years (range 25–87).

Data on the size of the primary tumour and rete testis involvement at initial diagnosis are available on 173 of the patients. These data are shown in Table 1.

mortality
There was no excess mortality in the carboplatin cohort compared with age- and sex-matched general UK population data (SMR for all-cause mortality 0.89; 95% CI 0.36–1.83) (Table 2). No patient died from testis cancer, although there were five new contralateral testis cancers and four testis cancer relapses. The seven deaths which occurred were due to cancer (n = 2), cerebrovascular disease (n = 2), suicide (n = 1) and ischaemic heart disease (n = 2) (Table 3). There was no specific time period (e.g. >5 years or 10 years) associated with increased mortality.

There was no significant increase in circulatory diseases as a cause of death in this cohort (SMR 1.44; 95% CI 0.39–3.69). In particular, there was no significant excess mortality for circulatory disease during the later time periods (>5 or 10 years after treatment). There were no significant increases in mortality for subsets of circulatory diseases, such as ischaemic heart disease or cerebrovascular disease (Table 2), although an SMR of 4.59 (95% CI 0.56–16.6) was observed for the latter, which requires further investigation. The deaths due to circulatory disease occurred 0.7–11.3 years after carboplatin treatment. The age of these patients at the time of death varied between 44 and 57 years.

incidence of second cancers
To date there has been no excess in the incidence of second cancers (other than testis cancer) (SIR 0.96; 95% CI 0.26–2.45) (Table 4). Additionally, there was no increase in the incidence of...
AUC, area under curve; NA, not available.

Meningioma AUC 7 87 7.7 NA

Myocardial infarction AUC 7 44 0.7 Smoker (25 pack-years)

Small-cell lung cancer AUC 7 87 13.9 Smoker (40 pack-years)

Berry aneurysm AUC 7 48 6.2 Hypertension

Myocardial infarction AUC 7 56 11.3 Smoker (pack-years NA)

Stoke AUC 7 47 10.2 NA

Suicide AUC 7 63 5.2 NA

Meningioma AUC 8 72 7.7 NA

AUC, area under curve; NA, not available.

Table 4. Incidence of second cancers after single-agent carboplatin

<table>
<thead>
<tr>
<th>Site</th>
<th>Interval</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testis cancers</td>
<td>0–5</td>
<td>0.09</td>
<td>0.00</td>
<td>0.00–42.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5+</td>
<td>0.08</td>
<td>60.27</td>
<td>19.57–140.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10+</td>
<td>0.03</td>
<td>34.07</td>
<td>0.86–189.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.17</td>
<td>29.57</td>
<td>9.60–69.01</td>
<td></td>
</tr>
<tr>
<td>Other solid cancers (excluding testis)</td>
<td>0–5</td>
<td>1.04</td>
<td>0.00</td>
<td>0.00–3.55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5+</td>
<td>2.60</td>
<td>1.15</td>
<td>0.24–3.37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10+</td>
<td>1.30</td>
<td>0.77</td>
<td>0.02–4.27</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>3.64</td>
<td>0.82</td>
<td>0.17–2.41</td>
<td></td>
</tr>
<tr>
<td>Haematological</td>
<td>0–5</td>
<td>0.19</td>
<td>0.00</td>
<td>0.00–19.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5+</td>
<td>0.35</td>
<td>2.88</td>
<td>0.07–16.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10+</td>
<td>0.16</td>
<td>0.00</td>
<td>0.00–22.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.54</td>
<td>1.86</td>
<td>0.05–10.38</td>
<td></td>
</tr>
<tr>
<td>All sites, excluding testis</td>
<td>0–5</td>
<td>1.23</td>
<td>0.00</td>
<td>0.00–3.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5+</td>
<td>2.95</td>
<td>1.36</td>
<td>0.37–3.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10+</td>
<td>1.47</td>
<td>0.68</td>
<td>0.02–3.80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>4.17</td>
<td>0.96</td>
<td>0.26–2.45</td>
<td></td>
</tr>
</tbody>
</table>

SIR, standardised incidence ratio; CI, confidence interval.

Table 3. Characteristics of the patients who have died

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Dose of carboplatin</th>
<th>Age at death</th>
<th>Follow-up since carboplatin (years)</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>AUC 7</td>
<td>44</td>
<td>0.7</td>
<td>Smoker (25 pack-years)</td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>AUC 7</td>
<td>87</td>
<td>13.9</td>
<td>Smoker (40 pack-years)</td>
</tr>
<tr>
<td>Berry aneurysm</td>
<td>AUC 7</td>
<td>48</td>
<td>6.2</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>AUC 7</td>
<td>56</td>
<td>11.3</td>
<td>Smoker (pack-years NA)</td>
</tr>
<tr>
<td>Stroke</td>
<td>AUC 7</td>
<td>47</td>
<td>10.2</td>
<td>NA</td>
</tr>
<tr>
<td>Suicide</td>
<td>AUC 7</td>
<td>63</td>
<td>5.2</td>
<td>NA</td>
</tr>
<tr>
<td>Meningioma</td>
<td>AUC 8</td>
<td>72</td>
<td>7.7</td>
<td>NA</td>
</tr>
</tbody>
</table>

second cancers during any specific follow-up period (>5 or 10 years). When haematological and solid tumours were assessed separately, neither was significantly increased, although the CIs were wide. An excess of contralateral testis cancers occurred separately, neither was significantly increased, although the CIs were wide. An excess of contralateral testis cancers occurred, with a patient with Hodgkin’s lymphoma. These tumours occurred 6.7–13.7 years after adjuvant treatment and all were histological confirmed. The patients with small-cell lung cancer and the patient with the meningioma received standard care, but both have died of their disease. The other two patients are alive and well, after a radical prostatectomy for prostate cancer and standard chemotherapy for Hodgkin’s disease.

**details of patients with recurrent contralateral testis cancer**

Five patients developed a second primary testis cancer (5.8–11.4 years after the initial testis cancer and carboplatin therapy). All had seminoma at histology. Four of the patients had stage I disease and one had metastatic disease to the para-aortic lymph nodes. The patients with stage I disease were treated with orchidectomy and were not given adjuvant treatment for a second time. All these patients are alive and disease free, with a median follow-up of 6.1 years after second testis cancer.

**details of patients with relapsed testis cancer**

Four patients have relapsed with metastatic seminoma 2–6 years after the initial diagnosis and carboplatin therapy. Three of these patients had initially received one cycle of carboplatin, and the remaining patient had received two cycles. Two of these patients relapsed with disease confined to the para-aortic lymph nodes, one had additional lung metastasis and the remaining patient had extrapulmonary metastasis (liver). Consequently, three were IGCCCG (International Germ Cell Cancer Collaborative Group) good-risk disease while the remaining patient had intermediate-risk disease. All were treated with standard cisplatin-based combination treatment (BEP) and are alive and cancer free (3–12 years follow-up after BEP).

**discussion**

The lack of long-term outcome data is one of the factors limiting the use of adjuvant carboplatin in stage I seminoma [17]. The data presented here address this issue for the first time. The results are cautiously reassuring, in that this treatment does not appear to be associated with an excess in overall mortality, cardiovascular mortality or second malignancies (other than testis cancer) in this observational period.

Previous work has shown that men treated with all types of chemotherapy for testis cancer have an increased risk of mortality from other causes when compared with the general population [15], although the increased risks they found were modest (SMR 1.34; 95% CI 1.15–1.55). Due to the comparatively small numbers involved, a small increase in mortality cannot be excluded in the current study. However, the mortality data presented here (SMR 0.89; 95% CI 0.36–1.83) are nevertheless reassuring and exclude any major increase in mortality associated with single-agent carboplatin.

Additionally, this work indicates that carboplatin is not associated with an increase in the development of second cancers during this observation period. Combination chemotherapy for testis cancer has been associated with the development of haematological cancers and solid tumours [7, 9, 10]. Indeed, the combination of chemotherapy and radiotherapy given together in testis cancer appears to increase this risk further [7]. The effect, however, appears to be drug specific, and platinum analogues have not been implicated previously in testis cancer, although they are associated with the
development of malignancies in preclinical studies [23]. Additionally, data from patients treated with platinum analogues for ovarian cancer indicate a small increased risk is present [24].

Long-term follow-up shows radiotherapy treatment for testis cancer is associated with an increase risk of second tumours [6–10]. This peaks between 10 and 20 years of follow-up. This relative risk is approximately double compared with age-matched controls. Recently, there have been modifications of the dose and extent of radiotherapy field [25, 26]. The effect this has had on the long-term risk is unknown, although it is speculated that it may have already reduced the incidence of second cancers [7].

In view of the fact that the second cancers peak 10–15 years after treatment with radiotherapy and only 45% of the patients in this study presented here have follow-up beyond this point, it is possible that these results may have underestimated the true risk. Therefore, we went on to specifically look at those individuals with >10 years of follow-up after treatment, and although the numbers are smaller, no specific increased risk could be identified (Tables 2 and 4).

The long-term risk of developing a contralateral testis cancer after a previous seminoma is ~2%–5%. This usually occurs within the first 6 years and decreases with time [27]. Previous data show that carboplatin is associated with a reduced risk of contralateral testis cancer in the first 4 years of follow-up, compared with radiotherapy (0.3% versus 1%) [13]. Our data, however, indicate that carboplatin is associated with a persistent long-term risk of contralateral testis cancer after 5 years of follow-up (4%). This finding is intriguing. The initial reduction in risk associated with carboplatin was thought to be because of the effects of carboplatin on carcinoma in situ in the remaining testis [13]. The data presented here indicate that carboplatin may be associated with a delay in the development of cancer in the contralateral testis rather than preventing it. This needs confirmation, but highlights the need for continued follow-up of these patients.

Only one (0.06% per annum) patient has relapsed with metastatic disease after 5 years of follow-up. Late relapses have been reported previously for patients with seminoma and this figure does not appear excessive compared with previous data [16]. This is reassuring and helpful in planning long-term follow-up for these patients. It is especially important as long-term cross-sectional imaging (computed tomography) is recommended beyond 5 years by some centres, if the risk of recurrence remains >0.3% per annum [16]. In our institution, we do not routinely carry out cross-sectional imaging beyond 2 years. Therefore, it is possible that we have missed some relapses which have resulted in an underestimation of the true relapse rate. If this was, however, the case, one would expect these patients to present eventually, with more advanced disease. This does not appear to be the case here. Nevertheless, this should be taken into consideration when interpreting this data.

Both radiotherapy and combination chemotherapy are associated with a long-term increased risk of cardiovascular disease in patients treated for testis cancer [11, 12, 15]. The data presented here indicate that this may not be the case with single-agent carboplatin. The one area of concern is cerebrovascular disease, where a nonsignificant increase was observed after 5 years of follow-up. This requires further investigation and underlines the need for continued follow-up of these patients.

Although limited by its size, this study helps address some of the concerns surrounding the long-term safety of single-agent carboplatin treatment for stage I testis cancer. It also helps plan long-term follow-up for these patients, especially in view of the contralateral relapses observed after 5 years of follow-up.

**Acknowledgements**

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**References**


