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Equivalence of cisplatin and carboplatin-based chemoradiation for locally advanced squamous cell carcinoma of the head and neck: A matched-pair analysis

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SUMMARY

Background: Carboplatin can be substituted for cisplatin in concomitant chemoradiation (CRT) for locally advanced squamous cell carcinoma of the head and neck (LASCCHN) when the latter is contraindicated. This matched-pair study aimed to compare the efficacy and acute toxicity of carboplatin and cisplatin.
Methods: Patients treated with 2 cycles of concomitant carboplatin-based CRT were matched to patients treated with 2 cycles of cisplatin. Matching criteria included age, tumour site, stage, smoking status and use of induction chemotherapy. Radiation was delivered using conformal techniques. Data on weekly acute toxicity throughout CRT was compared using the chi-squared test for proportions. Kaplan Meier statistics described time to local relapse, distant relapse and overall survival, the log-rank test was used to compare 3-year survival outcomes.
Results: Sixty-five patients who received carboplatin were matched to 65 who received cisplatin. Significant differences in toxicity included increased emesis with cisplatin and more anaemia and thrombocytopenia with carboplatin. There was no significant difference in 3-year locoregional control (87% vs. 79%, $p = 0.54$), freedom from distant metastases (88% vs. 85%, $p = 0.79$) and overall survival (59% vs. 68%, $p = 0.24$) between the carboplatin and cisplatin cohorts, respectively.
Conclusions: When cisplatin is contraindicated, carboplatin-based CRT yields equivalent treatment outcomes in patients with LASCCHN.

Background

Concomitant CRT is a treatment of choice for patients with locally advanced (stages III/IV) squamous cell carcinoma of the head and neck (LASCCHN). An absolute survival benefit of 6.5% for the addition of concomitant chemotherapy has been reported in a recent meta-analysis.[1] CRT may be used following induction chemotherapy as a part of a sequential organ-conserving approach or in a post-operative setting. In the latter context, a survival benefit has been shown in patients with high-risk features for recurrence, such as positive tumour resection margins and/or extra-capsular spread.[2,3]

Cisplatin is the cytotoxic agent of choice in concomitant CRT for LASCCHN. 2-year local control rates of 71% and an overall survival of 63% have been reported for primary CRT.[4] However, cisplatin may be contra-indicated in patients with pre-existing auditory problems, peripheral neuropathy and/or nephrotoxicity. In this setting, there is currently uncertainty regarding the best choice of concomitant agent. Carboplatin is frequently used to replace cisplatin because of its similar mode of action, but with lower rates of ototoxicity, nephrotoxicity, neurotoxicity and emesis.[5] However, large randomised trials using modern chemotherapy schedules that compare its efficacy and toxicity profile to cisplatin are absent from the literature.

At our centre, cisplatin is replaced with carboplatin in patients with ototoxicity and/or nephrotoxicity.[6,7] We have previously reported our experience with concomitant cisplatin for treatment of LASCCHN.[4] Here we present the results of a matched-pair analysis comparing concomitant cisplatin with carboplatin during radical CRT.

Patients and methods

Patient selection

All patients treated with radical concomitant CRT using 2 cycles of carboplatin for LASCCHN between January 2000 and December

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2010 were identified from pharmacy records. This included patients treated with induction chemotherapy followed by primary CRT and patients receiving post-operative CRT. A second cohort of patients treated with 2 cycles of concomitant cisplatin during the same time period was also identified for the purposes of matching. All patients with nasopharyngeal cancer or non-squamous cell cancer of the head and neck were excluded. This study was approved by the Committee for Clinical Research (CCR) and Research Ethics Committee at our institute.

Chemotherapy

Patients in the carboplatin cohort received two cycles of carboplatin at AUC5 on days 1 and 29 of radiotherapy. Patients receiving concomitant cisplatin received a dose of 100 mg/m^2 on the same days during radiotherapy. For patients receiving induction chemotherapy, the standard regimen was 2 cycles of platinum-based chemotherapy (cisplatin 75 mg/m^2 or carboplatin AUC5 on day 1) followed by 4 days of 5-fluorouracil 1000 mg/m^2 daily, given on a 21-day cycle. Carboplatin was used instead of cisplatin in patients with evidence of ototoxicity (hearing impairment or tinnitus) or reduced glomerular filtration rate (less than 50 ml/min).

Radiotherapy

Patients were immobilized and contrast-enhanced CT scans were acquired at 2.5 mm intervals. Gross tumour volume (GTV), clinical target volumes (CTVs) for macroscopic disease (CTV1), areas at risk of harbouring microscopic disease (CTV2) and critical structures were outlined. In patients requiring post-operative treatment, the tumour bed and the involved cervical lymph node levels were delineated as CTV1.

Radiotherapy was delivered using 3-D conformal radiotherapy or intensity modulated radiotherapy. CTV1was treated to a dose of 65 Gy in 30 fractions over 6 weeks. CTV2 was treated to a dose of 50 Gy in 25 fractions (54 Gy in 30 fractions over 6 weeks when using IMRT) over 5 weeks. For post-operative radiotherapy, CTV1 received a dose of 60 Gy in 30 fractions over 6 weeks in patients with a R1 (1–5 mm resection margin) resection and 65 Gy in 30 fractions over 6 weeks in patients with R2 resection (<1 mm (positive) resection margin).

Outcome measures

Data on patient demographics, tumour site and stage and smoking status were collected. For patients with orophyaryngeal tumours, immunohistochemical expression of p16 was used to assess human papillomavirus (HPV) status. The number of cycles, type of chemotherapy and reason for choice of carboplatin vs. cisplatin was recorded. Response rates to induction chemotherapy and CRT were assessed clinically and radiologically (using RECIST criteria, version 1.0[8]). A complete response was defined as no clinical or radiological evidence of disease 3 months after completion of CRT. Patients with residual disease at 3 months were referred for salvage surgery including neck dissection.

Toxicity outcomes were graded 0–4 according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, weekly during CRT and for 8 weeks after completion of radiotherapy. Toxicity outcomes measured included dermatitis, mucositis, dysphagia, nausea and vomiting, ototoxicity and neuropathy. Routine baseline audiometry was not performed and ototoxicity was evaluated by regular clinical assessment of tinnitus and/or hearing loss. Haematological outcomes measured included haemoglobin, absolute neutrophil count and platelet level. Glomerular filtration rate was measured at baseline, after two cycles of induction chemotherapy and if there was a significant deterioration in serum creatinine, which was regularly monitored.

Loco-regional recurrence was defined as disease recurrence at the primary site and/or cervical lymph nodes. Time to disease progression was measured from date of diagnosis to date of first local or distant recurrence. Freedom from distant metastasis was measured from date of diagnosis to date of first distant recurrence. Overall survival was measured from date of diagnosis to date of death. All of the outcome data were retrospectively collected from the electronic patient records (EPR).

Statistical analysis

Patients in the carboplatin cohort were individually matched to patients in the cisplatin cohort. Matching criteria used were tumour site (oropharynx, oral cavity, hypopharynx, larynx, paranasal sinuses or unknown primary), stage (AJCC III or IV), age (less than 61 years or 61 years or greater), smoking status (current smoker or non-smoker) and whether CRT was given with induction chemotherapy in a radical setting or without induction chemotherapy in a post-operative setting. Where an exact match according to the above criteria was not possible, the method of minimisation was used to restrict differences between patients. In the situation of more than one exact match to a carboplatin patient, one cisplatin patient was randomly selected from all possible exact matches.

The chi-squared test for proportions was used to compare rates of toxicity of different grades between patients treated with carboplatin or cisplatin. Fisher's exact test was used when the frequency of any observed toxicity was less than 5.

Kaplan-Meier methods were used to describe time to local relapse, distant relapse and overall survival. Data for patients lost to follow-up were censored from the time of last follow-up. The log-rank test was used to compare differences in local relapse, distant relapse and overall survival between patients receiving concomitant carboplatin and cisplatin.

Results

Patient characteristics

Sixty-five patients were identified from pharmacy records who had achieved 100% compliance with both cycles of concomitant carboplatin and met the defined eligibility criteria for the study. A further cohort of 279 patients who received concomitant cisplatin was identified and used for the matched-pair analysis. Fifty-seven patients (88%) in the cisplatin cohort matched based on all chosen criteria. The remaining 8 (12%) patients were matched on 4 of the 5 criteria.

Baseline characteristics of patients in both cohorts are shown in Table 1. The median age was 59 years (range 27–82 years) in the carboplatin cohort and 58 years (range 35–78 years) in the cisplatin cohort. Primary site of disease and stage are shown in Table 1, as is the HPV status of oropharyngeal tumours. Thirteen patients (20%) in the carboplatin cohort and 17 patients (26%) in the cisplatin cohort were current smokers. The numbers of ex smokers were 25 patients (38%) in the carboplatin cohort and 22 patients (33.8%) in the cisplatin cohort. Immunohistochemical expression of p16 in oropharyngeal tumours showed that the HPV positive tumours were well balanced in each cohort. In the carboplatin cohort ($n = 34$) 18 patients (53%), were HPV positive, 7 patients (20.5%) were HPV negative and for 9 patients the HPV status was unavailable. In the cisplatin cohort ($n = 36$) 19 patients (53%) were HPV positive, 6 patients (16.7%) were HPV negative and for 11 patients (30.6% the HPV status was unavailable.