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Assessing feasibility, compliance and toxicity of concomitant chemo-radiotherapy in head and neck cancers in the Northern Territory: initial experience and challenges

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Abstract

Introduction: Comprehensive oncology services have recently been introduced in the Northern Territory (NT) enabling delivery of concurrent chemo-radiotherapy (CCRT) in locally advanced head and neck squamous cell carcinoma (LAHNSC). The purpose of this study is to assess feasibility, compliance and toxicity of CCRT in remote Australia. **Methods:** Chart review was conducted for all patients >18 years, with biopsy-proven LAHNSC, receiving curative intent CCRT between January 2010 and September 2012. **Results:** The study population comprised of 26 patients, 20 Caucasian and 6 Indigenous, having a median age of 58 years, with most common sites of involvement being the oropharynx ($n = 16$) and the oral cavity ($n = 6$). Major risk factors were smoking and alcoholism. Cardiovascular disease, viral hepatitis, latent tuberculosis and strongyloidosis were the major comorbidities. Fifty-eight per cent ($n = 15$) required assisted feeding. All patients received intensity modulated radiotherapy. Systemic therapy comprised of cisplatin or carboplatin/cetuximab. Most common acute (grade 3/4) toxicities were mucositis, dysphagia and dermatological in 54%, 31% and 23% respectively. Complications were infection and gastrostomy insertion related. Hospitalisation occurred in 23%, treatment break >2 days in 38%, with no difference in toxicities between indigenous and nonindigenous patients. Platinum use was associated with greater nausea ($P = 0.003$), renal dysfunction ($P = 0.03$) and ototoxicity ($P = 0.04$) and cetuximab with dermatological reactions ($P = 0.05$). At median follow-up of 16 months, overall survival was 58% with progression-free survival of 50%. **Conclusions:** We have demonstrated good compliance rates, tolerance and feasibility outcomes. The seeming preponderance of LAHNSC in the NT is cause for concern.

Introduction

The Northern Territory (NT) has a large indigenous and multicultural population living in a tropical environment. The remoteness of the Outback, comorbidities and the clinical settings encountered are unique in the Australian context and make the task of providing these complex treatments extremely challenging. Comprehensive oncology services have recently been introduced with the opening of the Alan Walker Cancer Care Centre (AWCCC) and the introduction of radiation oncology services. This has made it possible for patients to receive treatment in Darwin rather than interstate. Concurrent chemo-radiotherapy (CCRT) can be associated with significant morbidity which has the potential to cause major treatment delays and compromise outcomes. The

purpose of this study is to assess feasibility, compliance and toxicity of CCRT in remote Australia. An audit of treatment and its toxicities would enable identification of problem areas and tailor better management strategies.

During the past two decades, the treatment paradigm for locally advanced head and neck squamous cell carcinoma (LAHNSC) has rapidly evolved with CCRT, emerging as a current standard of care as definitive or adjuvant treatment. Unresectable LAHNSC has a poor prognosis and CCRT has demonstrated improvement in 5-year overall survival rates of 6.5% and lower local failure rates of 9.3% as compared to radiation therapy alone.[1–10]

A primary organ preservation approach with CCRT yields survival similar to laryngectomy followed by adjuvant radiotherapy with high rates of larynx preservation and excellent functional outcome.[11–14]

CCRT also provides improved local/regional control and overall survival in patients with high-risk LAHNSC after surgery compared to postoperative RT alone. Factors that define high risk include positive surgical margins, extra-capsular lymph node extension, involvement of multiple lymph nodes, perineural spread and lymphovascular space invasion.[15,16]

Materials and Methods

All patients over 18 years, with biopsy-proven LAHNSC who received curative intent CCRT between January 2010 and September 2012 for unresectable disease, organ preservation and postsurgery high-risk features were included in this study. All patients had 18 Fluoro-Deoxyglucose Positron Emission Tomography (PET) scan for staging prior to starting treatment at the Royal Adelaide Hospital.

All patients gave consent for therapy. Indigenous liaison officers were also employed for detailing treatment modalities to the indigenous patients. Ethics committee as well as the Aboriginal ethics subcommittee approval was granted for this study.

Chemotherapy regimens

The following regimens were used[1–17]:

- High-dose regimen (preferred): cisplatin, 100 mg/m^2 IV, given for three cycles every 21 days concomitantly with RT.
- Weekly regimen: cisplatin, 40 mg/m^2 IV, given weekly concomitantly with RT.
- Cetuximab (Epidermal Growth Factor Receptor Antagonist – Monoclonal antibody: also referred to as immunotherapy or targeted therapy) used in patients unable to take cisplatin: as loading dose: 400 mg/m^2 1 week before and 250 mg/m^2 weekly with radiation.
- Weekly Carboplatin AUC of 2 in cases intolerant to cisplatin or cetuximab.

Radiotherapy details

For all patients, radiotherapy was delivered as per Radiation Therapy Oncology Group (RTOG) guidelines with dose painted simultaneous phase intensity modulated radiotherapy. Patients were computed tomography (CT) simulated, with 2-mm CT scan slices used for imaging purposes, in a neutral head position with a thermo-plastic S-shaped mask and personalised Vak-lok cushion. Where appropriate PET and magnetic resonance imaging fusion was utilised to identify the target volumes. The gross tumour was treated to 70 Gy in 35 fractions with the high-risk echelon of nodes treated to 63 Gy in 35 fractions and low-risk uninvolved nodes treated to 56 Gy in 35 fractions. Planning target volumes at risk with a 5-mm margin were applied to each clinically marked volume. RTOG guidelines were used for defining organs at risk, applying a priority constraint to temporal lobes, brain stem, spinal cord, parotids, submandibular glands, temporo-mandibular joint, inner ear apparatus, mandible, thyroid, trachea, optics, oral cavity, constrictors and brachial plexus. Planning risk volumes were used for the spinal cord and brainstem utilising a 3-mm margin for added safety during plan optimisation. For postoperative radiotherapy, the dose fractionation varied from 66 Gy in 33 fractions for positive surgical margins, 60 Gy in 30 fractions to the surgical bed and 54 Gy in 30 fractions to the uninvolved nodes.

RTOG Acute Radiation Morbidity Scoring Criteria, EORTC/RTOG Criteria of Late Effects and The NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE) were used for defining toxicities.[18]

Statistical analysis

All statistical analysis was done using SPSS for Windows (Version 16.0., Chicago, IL, USA) and SPSS Inc. (Epi 6 software, CDC, Atlanta, GA, USA). Chi-square test was used to determine significance between categorical variables. Wilcoxon rank sum test was the nonparametric test of significance used to compare data between two groups (indigenous and nonindigenous, platinum and non–platinum use). All *P*-values were two sided, $P < 0.05$ was considered significant.

Results

The study population comprised of 26 patients (6 Indigenous and 20 Caucasian), having a median age of

58 years and presenting with mostly locally advanced, unresectable stage 4 disease. Most common sites of involvement were the oropharynx and the oral cavity. Major risk factors were smoking and consumption of alcohol. Assisted feeding was required in 15 (58%) patients with 12 undergoing percutaneous gastrostomy (Table 1).

Cardiovascular diseases, hypertension and viral hepatitis were the commonest comorbidities encountered besides latent tuberculosis and strongyloidosis (Table 2).

The three HbsAg-positive patients were given prophylactic lamivudine and the two patients with Hepatitis C serology positivity were monitored for reactivation. In patients who were tested positive for viral hepatitis, there was no transaminitis at presentation and there was no reactivation during or after chemotherapy. In patients detected to have latent tuberculosis, chest X-ray and clinical profile did not suggest active tuberculosis and they were placed on prophylactic isoniazid. There was no reactivation of tuberculosis either during or after treatment.

The two patients, who tested positive for strongyloidosis, were given a course of ivermectin before start of treatment. History of past cancers was evident in seven (27%) patients: four (15%) head and neck cancers and three (12%) skin cancers.

Table 1. Patient characteristics.

Characteristics	Number of patients
Patients	26
Indigenous	6
Caucasian	20
Median age (years) (range)	58 (39–72)
Gender (Male:Female)	25:1
Smoking	25 (96%)
Regular alcohol intake	19 (73%)
Site and stage	Number
Oral cavity	6 (23%)
Floor of mouth	3
Tongue	2
Oropharynx	16 (62%)
Tonsil	7
Base of tongue	3
Larynx	1 (4%)
Hypopharynx (pyriform sinus)	2 (8%)
Unknown	1 (4%)
Stage	
III	4 (15%)
IVa	19 (73%)
IVb	3 (12%)
Therapeutic indications	
Locally advanced	23 (88%)
Laryngeal preservation	1 (4%)
Post op high risk	2 (8%)
Gastrostomy feeding	12 (46%)
Nasogastric feeding	3 (12%)
Emergency tracheostomy	1 (4%)

Table 2. Comorbidities.

Comorbidity	Number of patients (%)
Hepatitis B	3 (12%)
Hepatitis C	2 (8%)
Heart disease	6 (23%) (5 Ischaemic heart disease, 1 Atrial fibrillation)
Depression	3 (12%)
Hypertension	7 (27%)
Strongyloidosis	2 (8%)
Latent tuberculosis	3 (12%)
Past cancers	7 (27%) (4 Head and Neck, 3 Skin)
Dental infections	3 (12%)
Opioid abuse	1 (4%)
Renal dysfunction	1 (4%)

Cisplatin was initiated in 14 patients who were considered fit for receiving such therapy (100 mg/m^2 every 3 weekly: 12 patients; 40 mg/m^2 weekly: 2 patients) (Table 3). Only five (36%) could complete all planned treatment. In addition, due to toxicities and adverse reactions, three (21%) patients had to be shifted over to cetuximab after the first dose of cisplatin (two on the 3 weekly and one on the weekly schedule). The remaining six patients, however, received two doses of cisplatin 100 mg/m^2. Thus, 11/14 (79%) patients received a reasonable therapeutic dose of cisplatin.

Cetuximab was planned as initial therapy in 12 patients. Only nine (75%) were able to complete all planned cycles. In one patient allergic hypersensitivity reaction in the first cycle resulted in shifting over to carboplatin. On account of severe rash and dermatological reactions, two patients on Cetuximab could not complete treatment.

All patients completed their prescribed course of radiation therapy. Median treatment time was 49 days. There was significant treatment delay >2 days in 10 patients (Table 4).

Table 3. Chemotherapy details.

Type of treatment received	Number of patients	Completed all cycles
Cisplatin	11	5 (45%)
Cisplatin 3 weekly 100 mg/m^2	9	4 (44%)
Cisplatin weekly 40 mg/m^2	2	1 (50%)
Cisplatin changed to Cetuximab	3	3
Cetuximab alone	11	9 (81%)
Cetuximab changed to carboplatin	1	1

Table 4. Radiation details.

Treatment characteristics Radiation dose	Value Number of patients (%)
70 Gray/35 fractions	21 (81%)
68 Gray/34 fractions	3 (12%)
60 Gray/30 fractions	2 (7%)
Completed planned treatment	23 (88%)
Treatment break (≥2 days)	10 (38%)
Treatment time (mean)	50.4 days
Treatment time (median)	49 days (42–61 days)
Treatment break (median)	4 days (2–12 days)

Table 5. Acute complications.

Complication	Grades 1–2 Number of patients (%)	Grades 3–4 Number of patients (%)
Mucositis	11 (42%)	14 (54%)
Nausea	8 (31%)	3 (12%)
Vomiting	9 (35%)	2 (8%)
Anorexia	9 (35%)	3 (12%)
Xerostomia	16 (62%)	2 (8%)
Dysphagia	12 (46%)	8 (31%)
Dysarthria	3 (12%)	0
Dysgeusia	13 (50%)	0
Fatigue	12 (46%)	3 (12%)
Dermatological reactions	8 (31%)	6 (23%)
Cetuximab related	5	3
Cisplatin induced renal dysfunction	4/14 (29%)	0
Ototoxicity (CDDP)	3 (12%)	0
Neutropenia	5 (19%)	0
Anaemia	5 (19%)	2 (8%)

Grade 3/4 toxicities were observed in 65% patients. Severe mucositis, dysphagia and skin toxicity were the most common (Table 5).

Severe dermatological reactions were seen in 23% patients. Dermatological reactions were seen in 8/15 (53%) patients exposed to cetuximab. Of these, five (33%) had mild reactions, whereas three (20%) developed severe dermatological reactions which were also associated with florid acneiform rash.

Xerostomia, dysphagia, fatigue, nausea and anorexia were also present in the majority of patients, but were mostly grade 2 or less (Table 5).

Renal dysfunction was seen in 4/14 patients (29%) given cisplatin. The renal dysfunction was reversible and resolved in a median of 2.25 (2–5 weeks). Ototoxicity was seen in 3/14 (21%) patients exposed to cisplatin (one had reversible tinnitus, whereas two patients had persistent hearing impairment). Mild (grade 1/2) neutropenia was seen in 19% cases (Table 5).

Gastrostomy-related complications were seen in 33% (4/12 cases). Leaks were observed in two patients and required reinsertion, whereas two patients developed gastrostomy site–related infections (*Methicillin-resistant Staphylococcus aureus* or *MRSA/Pseudomonas aeruginosa*) (Table 6).

Infectious complications were seen in a total of 11 (42%) patients (including those with gastrostomy site–related infections) (Table 6). In three patients, clinically serious infections including diabetic foot (*MRSA*), lobar pneumonia (*Streptococcus pneumoniae*) and peripherally inserted central catheter (PICC)-related thrombophlebitis were observed, which required hospitalisation. Overall, six (23%) patients were hospitalised.

There were two treatment-related mortalities: one patient had presumed unexpected sudden cardiac death at home within 2 weeks of finishing treatment, whereas another patient died of aspiration pneumonitis following osteo-radionecrosis 12 weeks after finishing therapy. Platinum use was associated with significantly greater nausea ($P = 0.003$), renal dysfunction ($P = 0.03$) and ototoxicity ($P = 0.04$). Cetuximab use resulted in more

Table 6. Infectious complications.

Other toxicities	Number of patients (%)	Grade/type	Comments
Gastrostomy-related complications	4/12 (33%)	Infections: 2 (*MRSA, Pseudomonas aeruginosa*), Leaks: 2	Reinsertion: 2
Other infections	9 (35%)		
Clinical	3 (12%)	Gingivitis 2, otitis externa 1	
Clinical + Microbiological	3 (12%)	Diabetic foot (*MRSA*sepsis) Pneumonia (*Streptococcuspneumoniae*) PICC thrombophlebitis (*MRSA*)	Hospitalisation required
Suspected fungal	3 (12%)	Oral candidiasis	
Aspiration	3 (12%)		

MRSA, methicillin-resistant *Staphylococcus aureus*; PICC, peripherally inserted central catheter.

Table 7. Long-term Complications and outcomes.

Toxicities	Number of patients (%)
Xerostomia	7 (27%)
Dysphagia	5 (19%)
Neck fibrosis	3 (12%)
Trismus	2 (8%)
Gastrostomy dependency	3 (12%)
Hearing loss	2 (8%)
Osteoradionecrosis	2 (8%)
Synchronous/metachronous malignancy	2 (8%)
Survival analysis	
Died	11 (42%)
Disease	9 (34%)
Complications	2 (8%)
Alive	15 (58%)
Without disease	13 (50%)
With disease	2 (8%)
Median follow-up	16 (5–32 months)

dermatological reactions ($P = 0.05$). There was no difference in toxicities between indigenous and nonindigenous patients.

Long-term toxicities

Persistent xerostomia and dysphagia were the major long-term toxicities (Table 7). Gastrostomy dependency was seen in three (12%) patients. Osteoradionecrosis was seen in two (8%), and two (8%) patients developed synchronous/metachronous malignancies (one head and neck/one lung).

At a median follow-up of 16 months (5–32 months), overall survival was 58% with a progression-free survival of 50%.

Discussion

This is the first such study from the NT. The challenges that needed to be overcome in providing this complex care included provision of housing and support programmes for patients from the Outback and remote communities, use of telehealth to prepare the patient prior to embarking on treatment, excellent team approach and effective communication among all the teams involved in cancer care (surgical, medical, radiation, dental, allied health, indigenous liaison officers and health workers). All patients coming from outside Darwin are provided residential accommodation in Darwin with regular shuttle services to bring them to the hospital. AWCCC has implemented a patient treatment model from inception that aims to address the social and cultural needs of indigenous patients. The model includes funded transportation, accommodation, meals and transfers from healthcare services to lodging for the patient and escort(s). Dedicated indigenous liaison officers and head and neck cancer care nurses aid in the practical aspects of treatment and are an essential component of patient care. Also, novel strategies including communication with family and friends through Skype are being implemented in an attempt to reduce isolation, particularly in those from remote communities. A number of factors, which negatively impact on compliance, can potentially be counteracted by a culturally sensitive model of care.[19]

The median age of 58 years was similar to the median age of 56–60 years observed in various studies.[1–17] The distinct male preponderance was also found in other study populations. Most patients in our study had stage 4 disease (85%) which was similar to the rates of 74–96% found in other studies.[1–17] Oropharynx was the commonest site for occurrence in 62% ($n = 16$), and was the predominant site in other studies as well with an incidence ranging from 56% to 69%.[1–3]

All patients planned for chemotherapy undergo screening with a Mantoux test for latent tuberculosis and serology for strongyloidosis. Strongyloidosis can be associated with widespread and life-threatening infection in the context of immunosuppression caused by chemotherapy.[20] Latent tuberculosis and strongyloidosis are somewhat unique propositions in the Australian context, but are very relevant for patient management in the NT because if untreated they can flare up during cancer treatment, adding to the comorbidity and causing significant treatment delays.

Only five (36%) of the patients originally started on cisplatin were able to complete all the prescribed courses of therapy. However, 11/14 patients (79%) received at least 200 mg/m^2 of cisplatin. Other studies have reported higher rates of patients receiving all three cycles: 49% to 61%.[15] In other studies, a similar proportion of patients received at least 200 mg/m^2 of treatment 66–84%.[1,15–17] We reported no grade 3/4 renal toxicities (only grade 1 and 2 toxicities), whereas other studies have reported these in 4–8.4%.[3,11] This could also partly be related to the practice of using cetuximab in patients deemed unfit for cisplatin.

Dermatological reactions (grade 3/4) were seen in only 3.8–7% of patients in studies employing cisplatin alone.[1,3,11,17] The high rates of dermatological reactions (23%) seen in our study mainly related to the use of cetuximab. This was similar to the 23% reported in the Bonner trial.[2] In our study 20% patients had severe acneiform rash and 8% patients had to discontinue cetuximab on account of the rash. The Bonner trial reported a similar 17% incidence of severe acenieform rash with 4.2% patients having to discontinue cetuximab. Hypersensitvity to cetuximab was seen in 4% ($n = 1$) of

our patients. In the Bonner trial, 1.8% of patients were not able to take cetuximab on account of hypersensitivity reactions.[2]

Assisted feeding was required in 57% which was comparable to rates of 51.5% seen in the Intergroup study.[3] High rates of gastrostomy-related complications were a cause for concern. Before the start of CCRT, this procedure was not done very frequently in Darwin. These cases were discussed in departmental meetings, the need for upgrading procedural skills was re-emphasised and feedback given to all concerned with the procedure. We also emphasised need for more frequent observation and cleaning and dressing of the insertion site, given the tropical and humid environment in which the patients are cared for. The purpose was to create awareness and use it as a quality indicator of therapy in order to avoid such complications in the future. Infections and leaks were the major causes of morbidity and hospitalisation.

Other studies have reported similar rates of hospitalisation – 21%[1] as compared to 23% in our study.

Overall grade 3/4 toxicity rates of 65% in our study were lower than those reported in other major studies – 77–91%.[11,15,17] There was no difference in toxicities between indigenous and nonindigenous patients. Mucositis was the commonest grade 3/4 toxicity encountered in 53.8% cases in comparison to 30.4–56% cases[1–3,15,16] in other studies, with some reporting an incidence as high as 76%.[17] Dysphagia was encountered in 31% cases and this was consistent with the rates of 24.5–35% described in other studies.[2,12,15,16] Nausea and vomiting were described in 12% of cases which was slightly lower than an incidence of 15.8–23% reported by others.[1,3,12,15,16] This could partly relate to the use of cetuximab in our study (as the Bonner trial reported an incidence of only 2% in their study)[2] as well as to the use of apprepitant and palonosetron in the antiemetic regimen for cisplatin.

Most studies have described grade 3/4 chronic toxicities in the range 20–30%.[2,12] In our study we encountered mostly grade 2 or less toxicities: the major being xerostomia (27%), dysphagia (20%) and neck fibrosis (12%) which have been described in up to 46%,[1] 26%[12] and 30%[1] in other studies.

The median treatment time in our study was 49 days which compared well with 52.5 days in the Intergroup study in unresectable patients where 85% patients were able to complete treatment.[3] One patient had a treatment delay of 12 days on account of severe dental infection and gingivitis requiring extensive antibiotic cover and tooth extraction highlighting the importance of dental health in treatment. Interestingly, in the Bonner trial, only 44% received treatment as planned, 31% had minor variation, 12% had acceptable major variation and 12% had unacceptable delays, whereas 9% could not be evaluated.[2] This highlights the complex interplay surrounding compliance to therapy in the face of complications and comorbidities which so accompany this form of therapy.

At a median follow-up of 16 months (5–32 months) overall survival was 58% with a progression-free survival of 50%. The Intergroup Trial reported a 3-year projected overall survival of 37%, with a median survival of 19.1 months, in the CCRT arm as opposed to 23% with a median survival of 12.6 months in the radiation alone arm ($P = 0.014$) in patients with unresectable disease.[3]

There seems to be a preponderance of LAHNSC in the NT (smoking and alcohol related): a cause for concern calling for further research and increased public awareness and education.

Conclusions

In this study, the first of patients treated in a remote oncology centre in tropical Australia, we have demonstrated good compliance rates and tolerance, similar to those described in the literature. This illustrates the ability of a centre in the NT, with attendant challenges, to develop a comprehensive head and neck chemo-radiotherapy programme, delivering excellent cancer care in the setting of regional and remote Australia. This study shows that bringing the treatment closer home to the remote communities, thus eliminating the tyranny of distance, is feasible.

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Conflicts of Interest

The authors declare no conflict of interest.

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