RESEARCH ARTICLE

Carboplatin/5-fluorouracil as an Alternative to Cisplatin/5-Fluorouracil for Metastatic and Recurrent Head and Neck Squamous Cell Carcinoma and Nasopharyngeal Carcinoma

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Abstract

Background: Palliative chemotherapy with cisplatin/5-fluorouracil (5FU) is the commonest regimen employed for metastatic and recurrent head and neck squamous cell carcinoma (SCCHN) and nasopharyngeal carcinoma (NPC). However, this regimen is cumbersome requiring 5 days of admission to hospital. Carboplatin/5FU may be an alternative regimen without compromising survival and response rates. This study aimed to compare the efficacy and toxicity of carboplatin/5FU regimen with the cisplatin/5FU regimen. Materials and Methods: This retrospective study looked at patients who had palliative chemotherapy with either cisplatin/5FU or carboplatin/5FU for metastatic and recurrent SCCHN and NPC. It included patients who were treated at UKMMC from 1st January 2004 to 31st December 2009 with either palliative IV cispaltin 75 mg/m^2 D1 only plus IV 5FU 750 mg/m^2 D1-5 infusion or IV Carboplatin AUC 5 D1 only plus IV 5FU 500 mg/m^2 D1-2 infusion plus IV 5FU 500 mg/m^2 D1-2 bolus. The specific objectives were to determine the efficacy of palliative chemotherapy in terms of overall response rate (ORR), median progression free survival (PFS) and median overall survival (OS) and to evaluate the toxicities of both regimens. Results: A total of 41 patients were eligible for this study. There were 17 in the cisplatin/5FU arm and 24 in the carboplatin/5FU arm. The ORR was 17.7 % for cisplatin/5FU arm and 37.5 % for carboplatin/5FU arm (p-value=0.304). The median PFS was 7 months for cisplatin/5FU and 9 months for carboplatin/5FU (p-value=1.015). The median OS was 10 months for cisplatin/5FU arm and 12 months for carboplatin/5FU arm (p-value=0.110). There were 6 treatment-related deaths (6/41=14.6%), four in the carboplatin/5FU arm (4/24=16.7%) and 2 in the cisplatin/5FU arm (2/17=11.8%). Grade 3 and 4 hematologic toxicity was also more common with carboplatin/5FU group, this difference being predominantly due to grade 3-4 granulocytopenia (41.6% vs. 0), grade 3-4 anemia (37.5% vs. 0) and grade 3-4 thrombocytopenia (16.6% vs. 0). Conclusions: Carboplatin/5FU is not inferior to cisplatin/5FU with regard to its efficacy. However, there was a high rate of treatment-related deaths with both regimens. A better alternative needs to be considered.

Keywords: Chemotherapy - cisplatin/5FU - carboplatin/5FU - SCCHN - NPC

Asian Pacific J Cancer Prev, **14 (2)**, 1121-1126

Introduction

The prognosis of patients with metastatic or recurrent squamous cell carcinoma of the head and neck region (SCCHN) is generally poor, with a median survival of 5-9 months, depending on patient and disease-related factors. Selected patients with good performance status and locally recurrent disease may benefit from surgical salvage and/or re-irradiation. For most patients with metastatic or advanced recurrent disease, treatment options include single agent chemotherapy, combination chemotherapy, targeted agents either alone or in combination with conventional chemotherapy, and best supportive care (Lane et al., 1968; Leone et al., 1968; Papac et al., 1978; Kirkwood et al., 1981; Pinto and Jacobs, 1991; Forastiere et al., 1992; Jacobs et al., 1992). Patients with recurrent nasopharyngeal carcinoma (NPC) may also be offered re-irradiation and/or nasopharyngectomy and/or neck dissection if they have only loco-regional disease but more often are given palliative chemotherapy especially if they present with metastatic disease. Although the aetiology and histology of NPC are different from SCCHN, the chemotherapy regimens used are similar. Survival rates for NPC patients who relapse with metastatic disease is also very poor with a median survival ranging from 5-12 months (Vikram et al., 1986; Leung et al., 1991; Yeo et al., 1996; Geara et al., 1997; Hui et al., 2004). The commonly used chemotherapy schedule are IV Cisplatin (CDDP) 75 mg/m^2 plus IV 5Fluorouracil (5FU) 750 mg/m^2 over 5 days infusion or IV Carboplatin AUC 5 plus IV 5FU

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500 mg/m^2 infusion over 2 days plus IV 5FU 500 mg/m^2 bolus for 2 days.

The main aim of chemotherapy in this setting besides improvement of survival would be for palliation. Response rate is an appropriate surrogate end point in this situation as it is an objective measure and we can expect better palliation when the response rates are higher. CDDP is probably the most active agent in SCCHN with a response rate between 20% and 30% (Jacobs et al., 1978; Writes et al., 1979; Writes et al., 1980). The standard treatment dose is 75 mg/m^2 to 100 mg/m^2 intravenously every 3-4 weeks. The common toxicities with CDDP include nausea, vomiting, nephrotoxicity, ototoxicity, neuropathy and myelosuppression but these toxicities are manageable if patients are appropriately screened before start of treatment, monitored closely during it and treated appropriately. Further dose escalation of CDDP had not been established to improve outcome. A randomized trial comparing 60 mg/m^2 versus 120 mg/m^2 of CDDP failed to demonstrate a significant improvement in response or survival (Sako et al., 1978; Veronesi et al., 1985). There were trials that also evaluated very high doses of CDDP up to 200 mg/m^2 using schedules of 40-50 mg/m^2 for 5 days (Forastiere et al., 1987; Havlin et al., 1989). Such doses attained response rate of 46% and 73% but was complicated by severe toxicities.

Carboplatin is another alternative platinum agent that is well studied and commonly used in SCCHN. It has less nephrotoxicity, ototoxicity, neurotoxicity and gastrointestinal toxicity than the parent drug and is also easier to administer. However, it is more toxic to the bone marrow. The Southwest Oncology Group (SWOG) evaluated carboplatin in a phase II trial in recurrent head and neck cancer and observed a 24% response rate as a single agent (Forastiere et al., 1992). It has also been tested in combination therapy with other chemotherapy and targeted agents in NPC. In combination with paclitaxel and gemcitabine, it yielded a response rate of 78% with a median overall survival of 18.6 months in a phase 2 trial (Leong et al., 2004). Another phase 2 trial tested it in combination with cetuximab, a targeted therapy against epidermal growth factor receptor which is expressed in most NPCs, in patients who had progressed on or within 12 months after termination of platinum based chemotherapy for recurrent or metastatic NPC. This trial yielded a response rate of 11.7% and the authors concluded that this combination demonstrated clinical activity with an acceptable toxicity profile in a heavily pretreated population (Chan et al., 2005). More recently, carboplatin has been compared to CDDP in the definitive setting with chemoirradiation for locally advanced NPC. This randomized trial compared CDDP 100 mg/m^2 days 1, 22 and 43 concurrently with radiotherapy versus carboplatin 100 mg/m^2 on days 1, 8, 15, 22, 29 and 36 concurrently with radiotherapy. Adjuvant chemotherapy with CDDP/5FU was then given for the former group and carboplatin/5FU was given for the latter group for a total of 3 cycles. There was no statistically significant difference in the disease free survival and overall survival at 3 years between the two groups but toxicity was more severe in the CDDP arm. There were more renal toxicity, leucopaenia and anaemia in the CDDP arm while the carboplatin arm had more thrombocytopaenia. The authors concluded that carboplatin based regimen is better tolerated compared to CDDP regimen (Chitapanarux et al., 2007).

Attempts at increasing the efficacy of chemotherapeutic agents by using them in combination have had limited success in patients with recurrent of metastatic SCCHN or NPC. Combination chemotherapy had demonstrated superior response rate compared to single agent chemotherapy but there has been no improvement in OS. Six randomized trial had compared the benefits of single agent chemotherapy to combination chemotherapy. Single agent CDDP was used as the control arm for 2 trials (Jacobs et al., 1992; Clavel et al., 1994), single agent methotrexate for 3 trials (Williams et al., 1976; Vogl et al., 1985; Clavel et al., 1994) and one trial included both single agent methotrexate and CDDP (Jacobs et al., 1990). These trials also showed that the platinum and infusional 5FU (CDDP/5FU) combinations were the most active regimens for recurrent and/or metastatic SCCHN with overall response rate as high as 47% and a complete response rate of 27%. Despite the improved response rates, the median survival across these trials was similar ranging from 5-9 months. A meta-analysis reported by Browman and Cronin in 1994 yielded similar conclusions; there were higher response rates but more toxicity with CDDP and infusional 5-fluorouracil compared to single-agent therapy, and difference in median survival was less than 1 month. These data do not support the routine use of CDDP-based combinations for patients with recurrent or metastatic squamous cell cancer. Combination therapy seems most appropriate for patients with a good performance and have significant symptoms for which the higher anticipated response rate may translate into better palliation. In these trials, CDDP was given at 100 mg/m^2 intravenously and 5FU given at 1000 mg/m^2 continuous infusion over 96 hours recycled every 3 weeks.

Single institution pilot trials of carboplatin and infusional 5-FU in recurrent head and neck cancer patients reported response rates of 32-48% (Calvert et al., 1986; Inuyama et al., 1998). A randomized control trial comparing carboplatin-5FU, CDDP-5FU and single agent methotrexate showed a response rate of 21%, 32% and 10% respectively. There was no difference in the median OS (Forastiere et al., 1992). However, the CDDP-5FU regimen reported the highest rates of hematological and non-hematological toxicities while single agent methotrexate was the least toxic.

Many of the same drugs and regimens used in the treatment of SCCHN are also active in NPC. The World Health Organization (WHO) subtypes II and III are more responsive to chemotherapy. However, there is a lack of randomized trials that examined the efficacy of chemotherapy in metastatic and/or recurrent NPC. Site-specific phase II studies reported major response rates of 70% or higher with regimens containing CDDP (Boussen et al., 1991; Choo et al., 1991; Marchini et al., 1991; Taamma et al., 1999). In a review of the Princess Margaret Hospital experience, 40 patients received single agent or non CDDP-based combination chemotherapy with response rate of 25% while thirty patients who received

CDDP-based combinations achieved a response rate of 70% (Choo et al., 1991). The median OS was 9 months for the entire group and there was no difference between the two arms. In a phase II trial involving 42 patients using carboplatin-5FU for patients with metastatic NPC, a response rate of 38% was achieved and the median OS was 12.1 months (Yeo et al., 1996).

Success in treatment of incurable advanced cancers is usually measured in terms of improvement in OS. Surrogate end-point such as response rate is a useful measure of efficacy for chemotherapy regimens but often do not translate into survival benefit. The more intensive regimes may have better responses but often with higher toxicity rates. The high doses of CDDP used in the trials were associated with increased toxicity. Emesis with CDDP is a major concern as patients with SCCHN often have poor oral intake and side-effects of nausea/vomiting would compromise this further. Infusional 5FU requires inpatient treatment over 5 days and 4 nights, and patients often require the use of chemoports due to thrombophlebitis secondary to 5FU. As CDDP/FU infusional regimes are given every 3 weeks, patients need to be in the hospital and away from their family for a significant amount of time. Given their short survival even with treatment, this is not ideal. Carboplatin-5FU is one such regimen which reduces hospital stay by half as infusional 5FU can be given over 48 hours and has not been shown to reduce the duration of survival. We have undertaken this review to determine our results in University Kebangsaan Malaysia Medical Centre (UKMMC) as we think that intensive chemotherapy in advanced SCCHN may have marginal benefits for patients in terms of responses and survival. Shorter time spent in hospital and less toxicity should also be the aims of palliative treatment. The gold-standard may need to be moved for patients with advanced SCCHN and NPC to provide balance between efficacy, toxicity and convenience. The aim of this study is to determine and compare the efficacy of palliative chemotherapy with carboplatin plus 5FU versus CDDP plus 5FU for patients with recurrent and metastatic head and neck cancer and NPC.

Materials and Methods

This is a retrospective study looking at patients who had palliative chemotherapy with either CDDP/5FU regimen or carboplatin/5FU regimen for recurrent and metastatic head and neck cancer and NPC that is not amendable to surgery or radiotherapy. This study included patients who were treated at UKMMC Clinical Oncology Department from 1st January 2004 to 31st December 2009 with either palliative IV CDDP 75 mg/m^2 D1 only plus IV 5FU 750 mg/m^2 D1-5 infusion or IV Carboplatin AUC 5 D1 only plus IV 5FU 500 mg/m^2 D1-2 infusion plus IV 5FU 500 mg/m^2 D1-2 bolus. The specific objectives were to determine the efficacy of palliative chemotherapy in terms of overall response rate (ORR), median progression free survival (PFS) and median OS and to evaluate the toxicities of both regimens. Survival data was obtained from the National Registry of Births and Deaths in September 2010. Response of tumour to chemotherapy was measured using WHO criteria. Complete remission (CR) was defined as the disappearance of all clinical evidence of tumour for a minimum of 4 weeks. Partial response (PR) was defined as a 50 % or more decrease in the sum of the products of longest diameters of measured lesions for a minimum of 4 weeks. Stable disease (SD) was defined as a steady state or a decrease in measurable lesions less than a PR without worsening of symptoms or the appearance of any new lesions for a minimum of 4 weeks. Progression disease (PD) was defined as equivocal increase of at least 25% in the size of any measurable lesion or appearance of new lesion. ORR is defined as the sum of complete response and partial response. Stable disease is considered as no response in this study. Difference between the response rates for these two regimens was tested for statistical significance with the Pearson's chi-square test. The main outcomes of this study were median PFS and OS. PFS was defined as from the start of palliative chemotherapy to the time of disease progression. Disease progression could either be distant metastasis, locoregional failure, local failure or death. OS was defined as from the start of chemotherapy to time of death from any cause. Patients who did not reach the endpoint or were lost to follow-up were censored. The PFS and OS were calculated using the Kaplan-Meier statistical analysis. Comparison between the CDDP/5FU and Carboplatin/5FU was done using the log-rank test. All analysis was done on SPSS version 16.0.

Results

A total of 41 patients with incurable head and neck cancer or NPC who underwent palliative chemotherapy in this institution were eligible for this study. Of the 41 patients, there were 17 patients in the CDDP/5FU arm and 24 patients in the Carboplatin/5FU arm. Table 1 summarizes the patients' characteristics in both arms. All the cases under review were above the age of 30 years. Amongst the group receiving CDDP/5FU, most of the patients were above 60 years old (47.1%). However, the carboplatin/5FU group showed a relatively equal distribution among all the age group. There was a predominance of male patients in both groups with 88% and 62% in the CDDP/5FU group and in the carboplatin/5FU group respectively. The most common ethnic group affected were the Chinese with almost equivalent proportions in both groups (70.6% and 79.2%). The study groups were well- balanced in terms of types of recurrences, number of metastatic cases and in terms of performance status.

Forty one patients were included in the analysis for response rate and survival. The ORR was 17.7% for CDDP/5FU and 37.5% for carboplatin/5FU. Pearson Chi Square showed that the difference was statistically not significant (p=0.304). Subset analysis showed that, of the 27 patients who had NPC 9 (33.3%) patients responded to treatment. Eight of them had Carboplatin/5FU and only 1 had CDDP/5FU. There were 14 patients with SCCHN of other sites and only 3 (21.4%) responded to chemotherapy. Two of these patients had CDDP/5FU and only 1 had carboplatin/5FU. The median PFS was 7

months for CDDP/5FU and 9 months for carboplatin/5FU (p-value=1.015). The median OS was 10 months for CDDP/5FU arm and 12 months for carboplatin/5FU arm (p-value=0.110). At the time of analysis, 38 patients had died where 31 died of progressive disease, 6 died of treatment-related complications and 1 patient committed suicide. More than half of the patients in the carboplatin/5FU group completed 6 cycles of chemotherapy. Out of the 11 patients who did not complete their treatment, 3 died during the treatment from neutropenic sepsis, 3 had progressive disease and 4 had their chemotherapy discontinued due to intolerable toxicity and one patient defaulted after 4 cycles of chemotherapy. In the CDDP/5FU group only 35.3% of the patients completed 6 cycles chemotherapy. This was because of 6 patients who had progressive disease while on treatment, 2 patients died during treatment and 2 patients stopped their chemotherapy due to toxicity.

Table 1. Patient Characteristics

		Cisplatin+5FU (N=17)		Carboplatin+5FU (N=24)	
		No	%	No	%
Age	31-40	3	17.6	2	8.3
	41-50	3	17.6	6	25
	51-60	3	17.6	9	37.5
	>61	8	47.1	7	29.2
Gender	Male	15	88.2	15	62.5
	Female	2	11.8	9	37.5
Race	Malays	3	17.6	5	20.8
	Chinese	12	70.6	19	79.2
	Indian	1	5.9	-	-
	Others	1	5.9	-	-
Alcohol	Yes	5	29.4	2	8.3
	No	12	70.6	22	91.7
Smoking	Yes	14	82.4	12	50
	No	3	17.6	12	50
Family history	Yes	-	-	7	29.2
	No	17	100	17	70.8
Site of disease	Oral cavity	1	5.9	1	4.2
	Larynx	1	5.9	1	4.2
	Hypopharynx	3	17.6	2	8.3
	Nasopharynx	8	47.1	19	79.2
	Paranasal sinus	-	-	1	4.2
	Ears	1	5.9	-	-
	Others	3	17.6	-	-
Initial treatment	Surgery	1	5.9	1	4.2
	CCRT	8	47.1	11	45.8
	Radiotherapy only	3	17.6	6	25
	No initial treatment	2	11.8	3	12.5
	Surgery +PORT	3	17.6	2	8.3
	Chemotherapy only	-	-	1	4.2
Types of recurrence	Local	9	52.9	12	50
	Regional Neck nodes	4	23.5	7	29.2
	Distant metastasis	4	23.5	5	20.8
Performance status	0	8	47.1	9	37.5
	1	6	35.3	11	45.8
	2	3	17.6	4	16.7

Table 2. Toxicities

	Cisplatin+5FU Grade (%)				Carboplatin+5Fu Grade (%)			
Toxicity	1	2	3	4	1	2	3	4
Anemia	70.6	23.5	-	-	20.8	33.3	33.3	4.2
Granulocytopenia	47.1	29.4	-	-	8.3	29.2	33.3	8.3
Thrombocytopenia	6	-	-	-	29.2	20.8	8.3	8.3
Nausea	70.6	23.5	-	-	33.3	8.3	-	-
Vomiting	64.7	17.6	-	-	25	12.5	-	-
Mucositis	5.9	11.8	-	-	8.3	-	-	-
Diarrhea	23.5	-	-	-	16.7	-	4.2	-
Neurotoxicity	11.8	-	-	-	16.7	-	-	-
Ototoxicity	-	-	-	-	12.5	-	-	-
Nephrotoxicity	5.9	5.9	-	-	8.3	4.2	-	-

A summary of adverse events associated with CDDP/5FU versus Carboplatin/5FU by National Cancer Institute Common Toxicity Criteria (Version 3) is presented in Table 2. There were 6 treatment-related deaths (6/41=14.6%), four in the carboplatin/5FU group (4/24=16.7%) and 2 in the CDDP/5FU group (2/17=11.8%). All had grade 3 or 4 hematologic toxicity that led to sepsis, except one who died of upper gastrointestinal bleeding secondary to Grade 4 thrombocytopenia. Grade 3 and 4 haematologic toxicities were more common with carboplatin/5FU group, this difference being predominantly due to grade 3-4 granulocytopenia (41.6% vs. 0), grade 3-4 anemia (37.5% vs. 0) and grade 3-4 thrombocytopenia (16.6% vs. 0). The difference between the two treatment arms with regards to anemia (p-value=0.013) and granulocytopenia (p-value=0.007) was statistically significant. Nausea, vomiting and diarrhea were the most frequently reported adverse side effects. CDDP/5FU was associated with more grade 1/2 nausea (94.1% vs. 41.7%) and grade 1/2 vomiting (82.4% vs. 37.5%). Carboplatin/5FU was associated with more grade 1 peripheral neuropathy (16.7% vs. 11.8%) and grade 1 ototoxicity (12.5% vs. 0%). However, these were not statistically significant. The rates of nephrotoxicity were almost equivalent in both arms (11.8 % vs. 12.5%). There was one patient with grade 3 diarrhea in the carboplatin/5FU group.

Discussion

This study represents an attempt to analyze the outcome of patients with recurrent and metastatic SCCHN and NPC at UKMMC who were treated with either CDDP/5FU or Carboplatin/5FU which are two of the commonest palliative chemotherapy regimens used in this institution. Results showed that carboplatin/5FU is non-inferior to CDDP/5FU in terms of ORR (37.5% vs. 17.7%), PFS (9 months vs. 7 months) and OS (12 months vs. 10 months), all of which were statistically insignificant.

Single institution pilot trials of carboplatin and infusional 5FU in recurrent SCCHN patients reported response rates of 32% to 48% (Forastiere et al., 1987; Olver et al., 1989). This study demonstrated a response rate of 37.5 %. Kish and colleagues (1985) reported a 70% ORR with 27% complete responses in 30 patients with recurrent and metastatic SCCHN treated with CDDP/5FU. Other single institution trials had tested this regimen and had yielded an ORR that varies between 11% and 79% (Al-Sarraf, 1988; Urba and Forastiere, 1989). Jacobs and colleagues (1990) compared CDDP/5FU with single agent CDDP and single agent 5FU which yielded an ORR of 32% for combination arm versus 17% for

single agent CDDP. The 17.7% ORR of CDDP/5FU arm demonstrated in our study was low and not different from results reported for single agent CDDP. This could be contributed by the fact that clinicians view CDDP/5FU as a very toxic regimen and resulted in a high percentage of dose reduction (23%).

The median OS in our study for CDDP/5FU regimen was 10 months and for the carboplatin/5FU regimen was 12 months. This is in line with other reported studies with a median OS ranging from 5-9 months for SCCHN and 5-12 months for NPC. The only prospective randomized study that compared CDDP/5FU with carboplatin/5FU showed a median OS of 6.6 months versus 5.0 months respectively which was not statistically significant for patients with advanced SCCHN (Forastiere et al., 1992). Our study shows that the carboplatin/5FU regimen will not compromise the survival of these patients when compared to the CDDP/5FU regimen.

The hematological toxicities were more pronounced for carboplatin/5FU in this study. There were more grade 3/4 toxicities especially granulocytopenia and luekopenia. There were also more treatment-related deaths (16.7% vs. 11.8%). These figures are worryingly high though the patient numbers were small. It could be that Asian patients may require a lower dose in this group of patients who already have a significant burden of disease. Moreover, the main aim of treatment is for palliation in which quality of life would be the main concern. A treatment-related death (TRD) rate of more than 5% in this group of patients would be difficult to justify its routine use for palliative intent if this was indeed the real rate. A much larger trial would be required to inform us of a better estimation of its TRDs. Certainly, this would instruct us to re-look at the dosage used and the need to inform patients of the very real risk of TRDs with these regimens. Non-hematological toxicities were reported more frequently in the CDDP/5FU group especially nausea and vomiting. However, these toxicities were confined to grade 1-2 toxicities. Moreover, with the advent of new anti-emetics like the serotonin-antagonists nausea and vomiting would not be a major problem.

This study shows that the carboplatin/5FU regimen can be used as a reasonable alternative to the CDDP/5FU regimen in this setting. It is not inferior to the CDDP/5FU regimen with regards to ORR, PFS and OS. The main advantage of this regimen is it only requires a 2 day infusion compared to a 5 days infusion with the CDDP/5FU regimen. This would be better for patients as they spend less time in the hospital and is cost-saving for both patients and the hospital. However, given the very high rate of TRDs for this regimen it cannot be recommended for routine use. A much larger trial with dose adjustment or a change in the regimen may be required. Bolus 5FU has been shown to be more toxic compared to infusional 5FU in the treatment for colorectal cancer especially with regards to hematological toxicity (Richard et al., 1996). The carboplatin/5FU regimen used in this study had 2 days of bolus 5FU and it may be necessary for the bolus 5FU to be discarded. The fear would be a less efficacious regimen as the total dose of 5FU would have been reduced. Another alternative would be to consider the usage of oral 5FU like capecitabine which has been shown to be at least as efficacious as bolus IV 5FU with less toxicity in colorectal cancer (Twelves et al., 2005). This has the added advantage that the regimen can be delivered as an outpatient regimen in the daycare center as IV carboplatin can be delivered as a one hour infusion and the oral 5FU can be taken at home. In fact, oral 5FU has been used in a few trials involving recurrent and metastatic SCCHN and NPC (Chua et al., 2002; Li et al., 2008; Won et al., 2011). Seventeen patients with recurrent or metastatic NPC previously treated with platinum-based chemotherapy were treated with oral capecitabine alone in a phase 2 study showed an ORR of 23.5% with no TRD (Chua et al., 2002). Another phase 2 study combined capecitabine with CDDP for patients with metastatic NPC. A total of 48 patients were enrolled into this study which showed a ORR of 62.5% with no TRD (Li et al., 2008). In the SCCHN setting, 36 patients with recurrent or metastatic disease were recruited for a phase 2 study utilizing palliative capecitabine and CDDP. This study yielded an ORR of 50% with no TRD (Won et al., 2011). It is conceivable for carboplatin to be added to capecitabine for this setting as it is easy to administer but this needs to be done in a trial setting to ensure it is efficacious and safe before it can be used in routine practice.

In summary, carboplatin/5FU is a suitable alternative to CDDP/5FU at least with regards to its efficacy. However, due to the high TRDs recorded in our study, dose adjustment and the use of prophylactic granulocyte colony-stimulating factor (G-CSF) is highly recommended. A better alternative needs to be considered.

References

Al-Sarraf M (1988). Head and neck cancer: chemotherapy concepts. *Semin Oncol*, **15**, 70-85.

Boussen H, Cvitkovic E, Wendling JL, et al (1991). Chemotherapy of metastatic and/or recurrent undifferentiated nasopharyngeal carcinoma with cisplatin, bleomycin, and fluorouracil. *J Clin Oncol*, **9**, 1675.

Browman GP, Cronin L (1994). Standard chemotherapy in squamous cell head and neck cancer: what we have learned from randomized trials. *Semin Oncol*, **21**, 311-9.

Calvert AH, Grumbrell LA, Henk MJ (1986). Paraplatin phase II studies in head and neck cancer. Proceedings from the Symposium on Paraplatin. The British Transition; London, England, p25.

Chan ATC, Hsu MM, Goh BC, et al (2005). Multicenter, phase 2 study of cetuximab in combination with carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. *J Clin Oncol*, **23**, 3568-76.

Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, et al (2007). Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: Randomised, non-inferiority, open trial. *Eur J of Cancer*, **43**, 1399-406.

Choo R, Tannock I (1991). Chemotherapy for recurrent or metastatic carcinoma of the nasopharynx. A review of the princess margaret hospital experience. *Cancer*, **68**, 2120.

Clavel M, Vermorken JB, Cognetti F, et al (1994). Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine versus cisplatin (CABO) and cisplatin+5FU versus cisplatin in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase II study of the EORTC head and neck cancer cooperative group. *Ann Oncol*, **5**, 521-6.

Forastiere AA, Metch B, Schuller DE, et al (1992). Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous cell carcinoma of the head and neck : a Southwest Oncology Group study. *J Clin Oncol*, **10**, 1245-51.

Forastiere AA, Natale RB, Takasugi BJ, et al (1987). A phase I-II trial of carboplatin and 5FU combination chemotherapy in advanced carcinoma of the head and neck. *J Clin Oncol*, **5**, 190-6.

Forastiere AA , Takasugi BJ, Baker SR et al (1997). High dose cisplatin in advanced head and neck cancer. *Cancer chemother Pharmacol*, **19**, 155-8.

Grose WE, Lehane DE, Dixon DO, et al (1985). Comparison of methotrexate and cisplatin for patients with advanced squamous cell carcinoma of the head and neck region: a Southwest oncology group study. *Cancer Treat Rep*, **69**, 577-81.

Hansen RM, Ryan L, Anderson T, et al (1996). Phase III study of bolus versus infusional 5 Fluorouracil with or without cisplatin in advanced colorectal cancer. *Ann Oncol*, **88**, 668-74.

Havlin KA, Kuhn JG, Myers JW, et al (1989). High-dose cisplatin for locally advanced or metastatic head and neck cancer. A phase II pilot study. *Cancer*, **63**, 423-7.

Hong WK, Schaefer S, Issell B, et al (1983). A prospective randomized trial of methotrexate versus cisplatin in the treatment of recurrent squamous cell carcinoma of the head and neck. *Cancer*, **52**, 206-10.

Inuyama Y, Togawa K, Morita, et al (1998). Phase II study of carboplatin in head and neck cancer. *Gan-To-Kagaku-Ryoho*, **15**, 2131-8.

Jacobs C, Bertino JR, Goffinet DR, et al (1978). 24-hour infusion of cisplatinum in head and neck cancers. *Cancer*, **42**, 2135-40.

Jacobs C, Lyman G, Velez-Garcia E, et al (1990). Liverpool head and neck oncology group. A phase III randomized trial of cisplatinum, methotrexate, cisplatinum +methotrexate and cisplatinum + 5FU in end stage squamous cell carcinoma of the head and neck. Liverpool head and neck oncology group. *Br J Cancer*, **61**, 311-5.

Jacobs C, Lyman G, Velez-Garcia E, et al (1992). A phase III randomized study comparing cisplatin and fluorouracil as single agent and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol*, **10**, 257-63.

Kirkwood JM, Canellos GP, Ervin TJ, et al (1981). Increased therapeutic index using moderate dose methotrexate and leucovorin twice weekly vs. weekly high dose methotrexate–leucovorin in patients with advanced squamous carcinoma of the head and neck: a safe new effective regimen. *Cancer*, **47**, 2414-21.

Kish JA, Ensley JF, Jacobs J, et al (1885). A randomized trial of cisplatin (CACP) + 5Fluorouracil (5FU) infusion and CACP +5FU bolus for recurrent and advanced squamous cell carcinoma of the head and neck. *Cancer*, **56**, 2740-4.

Lane M, Moore JE, Levin, et al (1968). Methotrexate therapy for squamous cell carcinoma of the head and neck. Intermittent intravenous dose program. *JAMA*, **204**, 561-4.

Leone LA, Albala MM, Rege VB (1968). Treatment of carcinoma of the head and neck with intravenous methotrexate. Cancer; 21, 828-837.

Leung SS, Wee J, Tay MH, et al (2004). Paclitaxel, carboplatin and gemcitabine in metastatic nasopharyngeal carcinoma. *Cancer*, **103**, 569-75.

Licitra L, Marchini S, Spinazzè S, et al (1991). Cisplatin in advanced salivary gland carcinoma. A phase II study of 25 patients. *Cancer,* **68**, 1874-7.

Li YH, Wang FH, Jiang WQ, et al (2008). Phase II study of capecitabine and cisplatin combination as first line chemotherapy in Chinese patients with metastatic nasopharyngeal carcinoma. *Cancer Chemother Pharmacol*, **62**, 539-44.

Morton RP, Rugman F, Dorman EB, et al (1985). Cisplatinum and bleomycin for advanced of recurrent squamous cell carcinoma of the head and neck: a randomized factorial phase III controlled trial. *Cancer Chemother Pharmacol*, **15**, 283-9.

Olver IN, Dalley D, Woods R, et al (1989). Carboplatin and continuous infusion 5-Fluorouracil for advanced head and neck cancer. *Eur J Cancer Clin Oncol*, **25**, 173-6.

Papac R, Minor DR, Rudnik S, et al (1978). Controlled trial of methotrexate and bacillus clamette-guerin therapy for advanced head and neck cancer. *Cancer Res*, **38**, 3150-3.

Sako K, Razack MS, Kalmins I (1978). Chemotherapy for advanced and recurrent squamous cell carcinoma of the head and neck with high and low dose cis-diamminedichloroplatinum. *Ann J Surg*, **136**, 529-33.

Taamma A, Fandi A, Azli N, et al (1999). Phase II trial of chemotherapy with 5-fluorouracil, bleomycin, epirubicin, and cisplatin for patients with locally advanced, metastatic, or recurrent undifferentiated carcinoma of the nasopharyngeal type. *Cancer*, **86**, 1101.

Twelves C, Wong A, Nowacki MP, et al (2005). Capecitabine as adjuvant treatment for stage III colon cancer (X-ACT trial). *N Engl J Med*, **352**, 2696-704.

Urba SG, Forastiere AA (1989). Systemic therapy of head and neck cancer: Most effective agents, areas of promise. *Oncology*, **3**, 79-88.

Veronesi A, Zagonel V, Tirelli U, et al (1985). High-dose versus low-dose cisplatin in advanced head and neck squamous carcinoma: a randomized study. *J Clin Oncol*, **3**, 1105-8.

Vogl SE, Schoenfeld DA, Kaplan BH, et al (1985). A randomized prospective comparison of methotrexate with a combination of methotrexate, bleomycin, and cisplatin in head and neck cancer. *Cancer*, **56**, 432-42.

Williams SD, Velez-Gracia E, Essence I, et al (1986). Chemotherapy for head and neck cancer. Comparison of cisplatin+vinblastine+bleomycin versus methotrexate. *Cancer*, **57**, 18-23.

Writes RE (1980). Chemotherapy of head and neck cancer. *Otolaryngol Clin North Am*, **13**, 515-20.

Writes R, Heller K, Randolph V, et al (1979). Cis-dichlorodiammineplatinum(II)-based chemotherapy as initial treatment of advanced head and neck cancer. *Cancer Treat Rep*, **63**, 1533-8.

Yeo W, Leung TW, Leung SF, et al (1996). Phase II study of the combination of carboplatin and 5-fluorouracil in metastatic nasopharyngeal carcinoma. *Cancer Chemother Pharmacol*, **38**, 466.

Yon YW, Park YH, Ahn MJ, et al (2011). A phase II study of combination chemotherapy with capecitabine and cisplatin in patients with metastatic or recurrent squamous cell carcinoma of head and neck. *Ann Oncol*, **22**, 417-23.