Combination gemcitabine and cisplatin chemotherapy for metastatic or recurrent nasopharyngeal carcinoma: report of a phase II study


Background: To evaluate the efficacy and toxicity of combination gemcitabine plus cisplatin (GC) chemotherapy in metastatic or recurrent nasopharyngeal carcinoma (NPC).

Patients and methods: Forty-four patients of Chinese ethnicity with metastatic or recurrent NPC received ambulatory GC chemotherapy every 28 days (gemcitabine 1000 mg/m² days 1, 8 and 15; cisplatin 50 mg/m² days 1 and 8). There were 40 male and four female patients with a mean age of 47.4 years. More than half (54.5%) of the patients had received either prior platinum-based chemotherapy and/or radiotherapy to target lesions.

Results: There were nine complete responses and 23 partial responses in the 44 patients, achieving an overall response rate of 73% (78% for the 41 assessable patients). The mean duration of response was 5.3 months. Improved subjective symptom-control scores were found in 78% of patients with pre-existing symptoms, while 64% of patients experienced improved general well-being scores. Toxicity was mainly hematological: grade III/IV anemia, granulocytopenia and thrombocytopenia were found in 11, 37 and 16% of cycles, respectively. With a median follow-up of 17.2 months, 62% survived 1 year while 36% were alive and progression free.

Conclusions: Gemcitabine plus cisplatin chemotherapy offers a satisfactory overall response rate, subjective patient improvement and safety profile for metastatic and recurrent NPC.

Key words: cisplatin, gemcitabine, phase II, metastasis, nasopharyngeal carcinoma, recurrence

Introduction

Nasopharyngeal carcinoma (NPC) is the most common head and neck cancer in Hong Kong [1] and parts of southern China. Over 1100 new cases were diagnosed in 1997 in Hong Kong, with a crude incidence of 24.6 per 100 000 for males [1]. Treatment will fail in locoregional or distant sites or both in over 50% of patients at 10 years [2, 3]. Chemotherapy with cisplatin or carboplatin as the most active and most frequently employed drugs, is often used to treat distant metastasis or advanced locoregional recurrence. Platinum-based chemotherapy has been reported in various studies to have an overall response rate ranging from 38% to 91%, with complete response (CR) rates of 4–22% [4–15]. Newer agents like paclitaxel have also been combined with carboplatin, producing response rates of up to 75% [15].

Gemcitabine (2′-deoxy-2′,2′-difluorocytidine monohydrochloride isomer) is a novel analog of deoxycytidine that inhibits DNA synthesis. Gemcitabine triphosphate, the active metabolite after cellular uptake, competitively inhibits DNA chain elongation, leading to DNA fragmentation and cell death. Experimental data, both in vitro and in vivo, suggest that the gemcitabine–cisplatin (GC) combination with an appropriate schedule (close sequence or simultaneous exposure of the two compounds) should interact synergistically [16]. The mechanism of this synergism may be due to the ability of gemcitabine to potentiate cisplatin cytotoxicity by inhibition of cisplatin-induced DNA interstrand cross-link removal.

The favorable toxicity profile of the GC combination has recently been confirmed in studies for both non-small-cell lung cancer [17] and bladder cancer [18]. A recent report in combining GC in advanced squamous cell carcinoma of head and neck demonstrated an overall response rate of 22.7% among 22 patients [19]. The scheme used in that particular study was 50 mg/m² cisplatin on days 1 and 8, with gemcitabine 800 mg/m² on days 1, 8 and 15 every 4 weeks. Given the

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encouraging response rate and tolerable toxicity profile, we tested the GC combination in a phase II study for recurrent NPC with either distant metastasis and/or local recurrence to evaluate the end points of response and toxicity. Cisplatin was to be given on two separate days together with gemcitabine to maximize their synergistic effects and to allow the ambulatory delivery of treatment for outpatients.

Patients and methods

Patients

Eligible patients were required to have recurrent undifferentiated or squamous cell NPC previously radically treated. They had to have clinically and/or radiologically measurable recurrence in distant sites or locoregional sites or both. Histological proof of the recurrence was not mandatory, although it was advisable in clinical situations when differentiation from another primary tumor was considered difficult. Bone-alone metastasis was not eligible for study entry. Prior neoadjuvant or concurrent chemotheraphy with primary radiotherapy, as well as prior salvage chemotherapy for previous recurrence, was also allowed. These chemotherapy regimens, mostly cisplatin-based, had to have been completed at least 6 months before study entry and had not to have included gemcitabine. For locoregional recurrence to be eligible, there had to have been a similar period of 6 months from any prior radiotherapy to study entry. All patients were required to have Karnofsky performance status of at least 70; age between 18 and 70 years; a white blood cell (WBC) count of at least \(10^9/l\) and a platelet count of \(10^9/l\). Adequate renal function with creatinine clearance of at least 50 ml/min, reasonable hepatic and cardiac functions, and sufficient nutritional and mental status were other entry criteria of the study. The study protocol had been approved by the Ethics committee of the institution. Informed written consent was obtained from all patients before enrollment. The study was conducted in accordance with the Helsinki Declaration of the World Medical Association.

Chemotherapy treatment

All patients were treated on an outpatient basis. Gemcitabine was administered at a dose of 1000 mg/m\(^2\) by intravenous (i.v.) infusion in 250 ml Normal Saline over 30 min on days 1, 8 and 15 of a 28-day cycle, preceded by bolus i.v. injection of 20 mg metoclopamide and 5 mg dexamethasone. Cisplatin 50 mg/m\(^2\) was given i.v. in 1 l Normal Saline over 2 h following gemcitabine infusion on days 1 and 8, again preceded by bolus i.v. injection of metoclopamide 20 mg, dexamethasone 5 mg and frusemide 20 mg. Patients received at least three cycles of chemotherapy before being formally assessed for response to determine whether they should complete a total of six cycles or more. Treatment discontinuation, however, could occur for disease progression or unacceptable drug toxicity or after achievement of best response. In responding patients, treatment could be continued for more than six cycles until there was no further clinical benefit from chemotherapy. Further local treatment, mainly to ‘consolidate’ the locoregional recurrence by either radiotherapy or even surgery, was allowed if judged by the investigators to be clinically indicated.

The dose of both drugs was reduced to 75% if the WBC count was \(2.0–3.0\times10^9/l\) and/or the platelet count was \(50–99\times10^9/l\) when chemotherapy was due. Both drugs were omitted if the WBC count was \(\leq2\times10^9/l\) or the platelet count was \(\leq50\times10^9/l\). Cisplatin was deferred by 1 week if the creatinine clearance fell below 50 ml/min. Substitution by carboplatin was not encouraged for possibly enhancing myelosuppression. Growth factor support was neither planned nor encouraged. During chemotherapy, blood counts were performed during each visit. Serum biochemistry screening for liver and renal functions and creatinine clearance measurements were done at least once every cycle.

Outcome measurement

Tumor measurements were obtained before each cycle of therapy in patients with clinically apparent disease and every three cycles in patients who required radiographic studies. The radiological assessment for response was performed by two independent radiologists, and clinical assessment by two independent oncologists. Standard WHO criteria for response assessment were used: (i) CR was defined as the disappearance of all known disease on at least two observations not less than 4 weeks apart; (ii) partial response (PR) was defined as a decrease of 50% or greater in the sum of the products of the perpendicular diameters of measurable bidimensional lesions on at least two observations not less than 4 weeks apart, without any evidence of disease progression; (iii) stable disease was defined as a steady state of disease less than a PR but not regarded as progressive disease as defined below; and (iv) progressive disease was defined as a 25% or greater increase in the overall sum of measurable lesions as described above when compared with baseline, or the appearance of new lesions.

WHO grading for various organ toxicity was recorded in every cycle. In addition, patients were asked to score their subjective sense of general well-being and severity of prevailing symptom(s) such as cough, dyspnea, abdominal distending pain and headache, etc. This was carried out before every cycle and at the conclusion of the chemotherapy by a 10-point visual analog scale (VAS). A maximum score (10 points) on the VAS indicated a perfect subjective sense of general well-being or complete freedom from a specified symptom due to NPC recurrence, which prevailed before study entry, while a low score (zero) indicated the extreme reverse end of the spectrum. These simplified measurements were used as approximate surrogates for quality of life assessment.

Statistical analysis

The primary end point was the objective response rate. The secondary end points were toxicity, progression-free survival, overall survival and VAS scores. Duration of response was measured from the date of the first observed response to date of disease progression or last follow-up. The study was designed to enroll at least 40 patients, based on the ‘null hypothesis’ \(H_0\) with a threshold response proportion of 0.35 and a desired alternative response proportion for rejection of \(H_0\) of 0.6. Using two-sided statistical hypothesis testing, the power was 0.9 for a type I error of 0.05. Survival was estimated by the Kaplan–Meier method and was measured from the date of study entry to the date of event or censor. The analysis was done according to the intention-to-treat principle. The statistical software SPSS for windows (version 9.0) was used for statistical analysis.

Results

From January 1999 to August 2000, 44 patients were enrolled into the study in a single institution. Clinical characteristics of the study patients are listed in Table 1. All patients were of Chinese ethnicity with a male predominance and Karnofsky performance score of at least 70. With a median interval of relapse of 30 months from the end of primary radiotherapy, the mean age of the patients (47.4 years) at study enrollment was consistent with the median age of NPC diagnosis in the
Chinese population. As expected, 98% of the tumors were undifferentiated carcinomas and only one patient had moderately differentiated squamous cell carcinoma. Approximately two-thirds of the patients possessed two or more recurrent sites. The majority of the recurrent sites were distant metastases (lung parenchyma, pleura, liver, lymphadenopathy below clavicles, bone, spleen) as only nine patients (20.5%) had locoregional recurrence (naso pharynx, nasal and paranasal sinuses, base of skull, retropharyngeal or neck lymph nodes) alone. The other 35 patients (79.5%) had distant metastasis with or without locoregional recurrence. Fifteen of the 44 patients (34%) had received a prior cisplatin-based combination at least 6 months before study entry. Fifteen patients also received prior radiotherapy to the target site(s) of recurrence, the majority of whom had locoregional recurrence with or without distant metastasis at study entry. Nine patients had both prior radiotherapy and chemotherapy. In summary, only 20 patients (45.5%) had no exposure to prior radiotherapy or chemotherapy. The median interval from prior chemotherapy or prior radiotherapy to target sites of recurrence among the 24 patients was 11.9 months.

Chemotherapy dosage

A total of 210 cycles of GC chemotherapy were given over a period of 28 months, delivering a median of five cycles per patient (range one to eight). Approximately half (48%) of the 44 patients received at least six cycles of chemotherapy as planned, while 12 patients (27%) received three or less cycles. Due to individual patient susceptibility and prior treatment, there was a delay in 8.6% of all cycles for day-1 and 11.9% of all cycles for day-8 injections according to preset guidelines. Similarly, day-1 and 8 injections of GC were omitted two (1%) and 16 times (7.6%), respectively, while day 15 of gemcitabine alone was omitted 73 times (34.8%) altogether. These resulted in delivering a mean dose intensity of 74% (554.3 mg/m²/week, range 315.0–763.4 mg/m²/week) for gemcitabine and 83% (20.6 mg/m²/week, range 8.6–25.0 mg/m²/week) for cisplatin. The equivalent mean relative total dose (RTD) (actual total dose/ideal total dose for the given number of cycles) is 0.78 (range 0.5–1.0) for gemcitabine and 0.87 (range 0.37–1.0) for cisplatin.

Chemotherapy toxicity

Hematological toxicity was the major dose-limiting toxicity as summarized in Table 2. WHO grade 3/4 anemia, neutropenia and thrombocytopenia were encountered in 11, 37 and 16% of all 210 cycles of chemotherapy. Although there was

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Total number of cycles graded accordingly (percent of total number of cycles in brackets).
more than one-third incidence of significant neutropenia, only
five episodes of neutropenic sepsis were documented (2.4% of
the 210 cycles) even when growth factor was never used for
marrow support. The median nausea/vomiting grading was 2
when hydroxytryptamine type 3 receptor (HT3) antagonists
were also not routinely prescribed. Twenty-eight patients
experienced a mean weight loss of 6.4% (range 0.8–16.3%) while 16 patients (36%) recorded a net gain or no change in
body weight after chemotherapy. Twelve patients reported
grade 1 and six a grade 2 peripheral neurotoxicity after chemo-
therapy, while no renal toxicity was recognized. Altogether,
34 hospital admissions were reported among 20 patients.
Blood transfusion, fever or infection, and gastrointestinal
upset represented more than 80% of the indications for the
hospitalization. One patient died of suspected reactivation of
chronic hepatitis B ~7 weeks from the end of chemotherapy.

**Chemotherapy responses**

Response data were not available in three patients. One patient
had concomitant pulmonary tuberculosis and was transferred
to the respiratory physicians for tuberculosis treatment after
the first cycle, and the patient died ~1 month later of tuber-
culosis without reassessment of his initial local relapse and
liver metastasis. Another patient, having liver and porta hepa-
tis lymph node metastases, refused to complete the first cycle
of chemotherapy as well as further radiological evaluation
before his demise from progressive bone metastasis 5 months
later. A third patient, who had bone-alone metastasis, pre-
sented with a significant soft tissue mass associated with rib
metastasis, which was initially mistaken as a lung metastasis
on chest radiography. The rib mass disappeared after six
cycles but a follow-up isotope bone scan produced a very dif-
cult and equivocal interpretation, and response assessment
was deemed impossible. As patients with bone-alone meta-
stasis were not eligible for the study, this patient, together with
the other two described above, was therefore considered not
assessable for response evaluation to avoid bias. There were
32 responses among the 41 assessable patients, contributing to
an overall response rate of 78%. As indicated in Table 3, the
overall response rate became 73% when all 44 patients were
included in response evaluation based on an intention-to-treat
principle. Among the 32 responders, there were nine CRs
(20.5%) and 23 PRs (52.3%). The mean response duration for
responders was 5.3 months. Nine patients did not achieve a
response but all of them had stabilization of disease (20.5%) and
none had disease progression.

Prognostic factors including age (≤45 versus >45 years), sex
(male versus female), Ho’s overall stage (1–3 versus 4–5),
first recurrence or not (yes versus no), site of recurrence (loc-
regional versus distant metastasis ± locoregional), recurrence
interval from primary radiotherapy (≤2 versus >2 years),
history of prior chemotherapy (yes versus no) and prior radio-
therapy (yes versus no) were examined in a binary logistic
regression analysis. None of them was shown to significantly
predict the occurrence of response in an individual patient.
There was no statistically significant difference (P value of
chi-square test = 0.082) between the response rates of loco-
regional disease alone (55.6%) and distant disease ± loco-
regional disease (84.4%). For patients who had prior exposure
to cisplatin-based chemotherapy (with or without radio-
therapy), 10 of 13 experienced responses to GC, while 22 of
28 patients without such an exposure had a response (P value
of chi-square test = 0.89). Similarly, there is no significant
difference in the proportion of GC responders between those
patients with, and those without, prior exposure to either
chemotherapy or radiotherapy or both (18 of 22 versus 15 of
18, P value of chi-square test = 0.93).

| Parameter | \( n \) (%)
|-----------|----------------|
| Overall response | 9 (20.5)
| Complete response | 23 (52.3)
| Partial response | 9 (20.5)
| Stable disease | 0 (0)
| Progressive disease | 3 (6.8)

| Response according to site among the 41 assessable patients | 5/9 (55.6)
|-------------------------------------------------------------|----------------|
| Locoregional alone | 20/24 (83.3)
| Distant alone | 7/8 (87.5)

**Patient scoring of well-being and symptom control**

Patients were asked to score their sense of general well-being
by a 10-point linear VAS before each cycle of chemotherapy
and at the conclusion of all chemotherapy. This was meant to
be a surrogate yardstick to measure the subjective impact of
chemotherapy on their general well-being upon alleviating the
prevailing symptoms and generating associated side-effects.
Out of the 43 patients with complete scores, 27 patients (63%)
recorded improved end-of-chemotherapy scores over pre-
chemotherapy scores. Unchanged and worse scores were
found in 11 (26%) and five (12%) patients, respectively.
Twelve of the 27 patients with improved scores had at least a
3-point (out of 10) improvement. The symptom severity
scores, measured in a similar fashion, were more specific in
purely assessing how effective the chemotherapy had control-
led the prevailing symptoms. Out of the 58 symptoms com-
pained of by the patients at study entry, 45 (78%), six (10%)
and seven (12%) symptoms were scored to become better,
unchanged and worse, respectively, after chemotherapy.
Twenty-seven of the 45 symptoms with improved scores had
at least a 3-point (out of 10) improvement. The 58 symptoms
complained of consisted of: cough (13), dyspnea (10), chest
pain (3), abdominal discomfort (6), axillary mass discomfort
Survival data
At a median follow-up of 17.2 months (range 6.9–26.8) from start of chemotherapy, 27 of 44 patients were still alive with the majority having disease. The median overall survival was 15.0 months. The actuarial overall survival at 1 year was 62%, while 36% survived at 1 year progression free. The median time to progression (progression-free survival) was 10.6 months (95% confidence interval 8.5–12.6 months). The overall survival and progression-free survival curves are presented in Figures 1 and 2, respectively. A Cox regression model was used to examine the relevant prognostic factors mentioned above. Relapse >2 years from the end of primary radiotherapy was shown to be a universally favorable prognostic factor for the two survival end points studied, probably indicating a more slowly progressive disease.

Discussion
Gemcitabine as a single agent has been used to treat distant or locoregionally recurrent NPC, producing a response rate of 43% [20]. We report an overall response rate of around 73% (with 20.5% CRs) among all 44 patients in this phase II study, and around 78% for the 41 assessable patients. The results were comparable with most reports in the literature employing ‘standard’ cisplatin-based chemotherapy [3–15]. The efficacy of the GC combination was therefore confirmed for the NPC endemic among subjects of Chinese ethnicity with a predominantly undifferentiated or non-keratinizing histology (WHO grade 2 and 3). These encouraging results were obtained irrespective of an exposure to prior cisplatin chemotherapy and/or radiotherapy in over half of the patients. It is interesting to note that similar chemotherapy produces a much lower response rate in previously untreated squamous cell carcinoma of the head and neck [19], indicating the higher chemosensitivity of NPC.

Despite an initially satisfactory overall response rate and a rather high CR rate, the mean duration of response for responders was brief (5.3 months). Therefore, it may not be illogical to give consolidation or maintenance therapy to those who respond after the planned six cycles. This is especially beneficial to (i) patients with only locoregional recurrence, in whom additional aggressive local therapy may serve to eradicate the drug-resistant clones, and (ii) those with limited thoracic disease whose long disease-free survival after aggressive combined therapy has been reported [21]. Indeed, four of the nine patients with locoregional recurrence alone received a second course of radiation after chemotherapy. Two other similar patients underwent surgery (nasopharyngectomy and radical neck dissection, respectively) for residual disease after chemotherapy that had reduced the initial extensive recurrence to an operable status. On the other hand, four patients had received more than six cycles of chemotherapy (three patients received seven cycles and one patient eight cycles) upon documentation of response. Whether continuation of similar chemotherapy for two or three more cycles beyond the planned six will improve the duration of response remains to be investigated in view of possible cumulative toxicity and patient’s diminishing tolerance.

Apart from achieving a high percentage of responses, the other advantage of this regimen is the ease of administration in the outpatient setting. The chemotherapy schedule was designed such that it could be given as outpatient treatment, thus obviating the costs and stress of hospital stay for the patient. The close sequential infusion of gemcitabine followed by cisplatin is based on experimental evidence of synergism [16] obtained with such a schedule and the clinical observation of satisfactory results in the treatment of various solid tumors. This synergism was taken advantage of fully by fractionating the cisplatin dose to allow two occasions of such sequential infusion of the two drugs within one cycle of chemotherapy. Such scheduling of sequential infusion proved
to be successful, as omission of day 1 or 8 infusions occurred in <10% of all cycles, although attenuation of the dose was inevitable in some of the cycles, leading to a mean RTD of cisplatin of 87%. The somewhat lower figure of 78% for the mean RTD of gemcitabine, due mainly to the 35% omission of the day-15 gemcitabine-alone infusion, can still be regarded as acceptable. In redesigning the strategy, one may consider giving a 21-day cycle consisting of only day 1 and 8 sequential infusions of GC but escalating the gemcitabine dose from 1000 mg/m² to 1250 mg/m². The possibility of continuing further chemotherapy as maintenance therapy beyond six cycles for responders should also be explored in future studies.

Finally, the fact that prior exposure (>6 months ago) to cisplatin-based chemotherapy did not adversely affect the probability of response may suggest the possibility of employing this combination regimen as second-line salvage chemotherapy for patients in whom first-line cisplatin-based chemotherapy has failed. The ease of administration and lack of significant toxicity positions itself favorably when compared with other second-line regimens such as ifosfamide–5-fluorouracil–leucovorin [22].

There was negligible neutropenic sepsis despite a 37% grade 3–4 neutropenia without growth factor support. Stringent follow-up, strict adherence to guidelines on antibiotic prophylaxis and appropriate dose reduction were the keys to achieving such a low morbidity rate. Routine prescription of potent antiemetics, which was not enforced mainly for economic reasons, might have further improved the emesis grading and possibly subjective general well-being. Other non-hematological toxicities of cisplatin, such as neurotoxicity or renal toxicity, were not significant problems with such a fractionated schedule. The mortality from suspected hepatitis B reactivation should have been prevented with the routinely available lamivudine prophylaxis [23] for all hepatitis B carriers to cover the chemotherapy period up to ~6 weeks after chemotherapy.

Since chemotherapy for metastatic or recurrent NPC is still essentially a palliative treatment for the majority of cases, quality of life measurement besides response and survival is an important end point. Unfortunately, this was not documented in any of the NPC chemotherapy reports in the literature. Due to the absence of a fully validated Chinese version of such a tool for evaluation, attempts were made to use approximate surrogates. A 10-point VAS was used firstly to assess the severity of symptom(s) that prevailed at study entry, and this was tracked throughout the chemotherapy till the end. A separate assessment was performed to assess the patient’s own subjective rating of his/her general well-being before each cycle of chemotherapy, which was supposedly a rating discounted by the individual’s chemotherapy side-effects. It was not surprising, therefore, to find a smaller proportion of patients feeling better (63% better scores) at completion of chemotherapy than the number of symptoms felt to be less disturbing to the patients (78% better scores). By the same token, the magnitude of absolute scores gained in symptom control was also higher: 60% of symptoms with improved scores had at least a 3-point increase while 43% of patients with improved well-being scores had such an increase. With all the inherent shortcomings of such an unrefined and unvalidated tool, the encouraging impression from the score profiles indicated that the chemotherapy generally conferred clinical benefits to the symptomatic patients and the chemotherapy side-effects had not negated a significant subjective gain in symptom control.

Conclusion

Combination GC chemotherapy given in this schedule is effective for metastatic and recurrent NPC, achieving a high response rate of 78% with a high proportion of CRs (22%) even when more than half of the patients were treated previously with prior chemotherapy or radiotherapy. It can be given as an ambulatory outpatient schedule, is only moderately myelotoxic even without growth factor support and has produced negligible neutropenic sepsis. The majority of patients actually felt better in terms of general well-being (63%) or symptom control (78%). Routine use of HT3 receptor antagonists is also expected to reduce cisplatin-related emesis and further improve the subjective well-being score. Given the respectable response rate and safe toxicity profile, GC combination chemotherapy should be tested in a randomized setting to compare it with other ‘standard’ platinum-based regimens for end points including quality of life.

References


