Palliative chemotherapy in carcinoma nasopharynx

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Abstract

Introduction: Nasopharyngeal carcinoma is a rare malignancy. We conducted an audit of systemic therapies received in palliative setting in carcinoma nasopharynx and studied their outcomes. **Methods:** Patients who underwent first-line palliative systemic chemotherapy between January 2014 and April 2017 for carcinoma nasopharynx at the department of medical oncology at authors' institute were selected for this analysis. Toxicities, responses, progression-free survival (PFS), and overall survival (OS) were analyzed. In addition, a Quality-Adjusted Time without Symptoms or Toxicity analysis with threshold utility analysis was performed. **Results:** Fifty-one patients were included in this analysis. The indication of palliative chemotherapy was locoregionally recurrent disease in 25 (49.0%) patients and metastatic disease in 26 (51.0%) patients. The overall response rate was 62.0% (n = 33). The median PFS was 225 days (95% confidence interval [CI]: 164–274 days) and median OS was 513 days (95% CI: 286–931 days). The restricted mean TOX state duration was 2.6 days (95% CI: 0.3–4.9), restricted mean TWiST duration was 219.2 days (95% CI: 184.0–254.4), and restricted mean REL duration was 74.3 days (95% CI: 38.1–110.4). **Conclusion:** Systemic cytotoxic therapy in nasopharyngeal cancers is associated with high response rates and clinically meaningful PFS; with low duration of time spent in adverse events.

Key words: Chemotherapy, nasopharynx, palliative, Quality-adjusted Time without Symptoms or Toxicity, systemic

Introduction

The incidence of nasopharyngeal carcinoma varies across the globe.[1,2] It is endemic in certain regions of East Asia, while it is uncommon in other parts of the world.[1,3] There also exists biological differences between the nasopharyngeal malignancies seen in these two regions. The World Health Organization (WHO) Grade 3 tumor is the predominant grade in the East Asian region, while Grade 1 is more common in the other parts of the world.[4] The limited number of patients across the globe has hampered research.

The bulk of the limited research reported from East Asian regions and the Western world has focused on curative patients. The incorporation of chemotherapy with radiation as concurrent[5-8] or as induction[9-13] or as adjuvant[14,15] has been the common theme of studies reported in the curative setting. Very few studies involving chemotherapy in noncurative settings have been reported, largely being retrospective or single-arm Phase II studies.[16-23] Recently, a randomized Phase III study was reported in the palliative setting by Zhang *et al*., comparing the classic cisplatin-5 fluorouracil regimen against gemcitabine-cisplatin regimen.[17] These limited studies have provided inadequate information and have not helped in guiding decisions when treating nasopharyngeal malignancies in palliative setting. Certain important questions such as composition of palliative regimen, number of cycles, benefit with first-line therapy, and its tolerance are unanswered in literature. To overcome some of these deficits, we decided to conduct an audit of systemic therapies received in palliative setting in carcinoma nasopharynx to address the limited information available in this setting.

Methods

Patient selection

Patients who underwent first-line palliative systemic chemotherapy between January 2014 and April 2017 for carcinoma nasopharynx at the department of medical oncology were selected for this analysis. Patients who did not opt for systemic therapy or who were referred for receiving therapy at native place were excluded from this analysis. Patients who had received some form of palliative chemotherapy outside and then came for continuation with us were also excluded from this analysis.

Data collection

Baseline characteristics, age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), comorbidity, grade of malignancy, stage of malignancy, presence of distant metastasis, previous treatment details, indication for systemic therapy, type of regimen, number of cycles, response in accordance with Response Evaluation Criteria in Solid Tumors version 1.1, toxicity in accordance with Common Terminology Criteria for Adverse Events version 4.03, date of progression, status at last follow-up, and subsequent therapy details were recorded in an Excel sheet.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 16 (SPSS Inc., Chicago, IL, USA) and RStudio (RStudio Team [2015], RStudio: Integrated Development for R. RStudio, Inc., Boston, MA, USA) were used for analysis. Descriptive statistics was performed. Continuous variables were described in terms of median and interquartile range, while categorical variables were described in terms of percentages with 95% CI. Progression-free survival (PFS) was defined as time in months from the date of start of therapy till either date of progression or date of death. Patients who had neither events were censored at the date of last follow-up. Overall survival (OS) was defined as time in months from the date of start of therapy till the date of death. Patients who were alive were censored at the date of last follow-up. Kaplan–Meier method was used for time-to-event analysis. Cox regression analysis was performed to identify factors affecting PFS and OS. $P \leq 0.05$ was considered statistically significant.

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Quality of Life without Symptom and Toxicity (QTWiST) analysis was performed.[18] Three health states, namely TOX state, TWiST state, and REL state were defined for this analysis. TOX state was defined as the calendar days spent in toxicity post start of chemotherapy but before progression or censoring for progression. TWiST state was the duration of PFS without the time spent in TOX state. REL state was defined as the duration spent post first progression till death. The mean QTWiST was calculated using the below-mentioned formula:

Mean QTWiST = μ_{TOX}* restricted mean TOX + μ_{TWiST}* restricted mean TWIST + μ_{REL}* restricted mean REL

Where μ_{TOX}, μ_{TWiST}, and μ_{REL} are utility scores for TOX, TWiST, and REL health states, respectively. As utility score values for head-and-neck cancers are unknown, QTWiST scores were calculated using a permutation and combination of values from 0 to 1 in 0.25 increment for μ_{TOX} and μ_{REL}. Score of 1 denotes time of perfect health, while a score of 0 denotes time period which is similar to death.

Results

Baseline characteristics

Fifty-one patients were included in this analysis [Figure 1]. The median age was 49 years (interquartile range [IQR]: 28–60 years). The male-to-female ratio was 2.19. Majority of the patients had ECOG PS 0–1 (n = 45, 88.2%). The indication of palliative chemotherapy was locoregionally recurrent disease in 25 (49.0%) patients, while it was metastatic disease in 26 (51.0%) patients. Previous treatment was received by 35 patients (68.6%). Twenty-four patients (47.1%) had previous exposure to platinum compounds. The median event-free period post last treatment was 8 months (IQR: 3–15 months).

Treatment received

The chemotherapy regimens received are shown in Table 1. The commonest regimen received was 3-weekly paclitaxel-carboplatin 18 (35.3%). Gemcitabine-platinum regimen was received by nine patients (17.6%). The median number of cycles received was 6 (IQR: 4–6). Response was evaluable in 45 patients and the overall response rate was 73.3% (33, n = 45). There was no statistical difference in response rate between gemcitabine-platinum and other chemotherapy regimens (P = 0.692) [Figure 1]. The reasons for stopping chemotherapy and its toxicities are shown in Table 2.

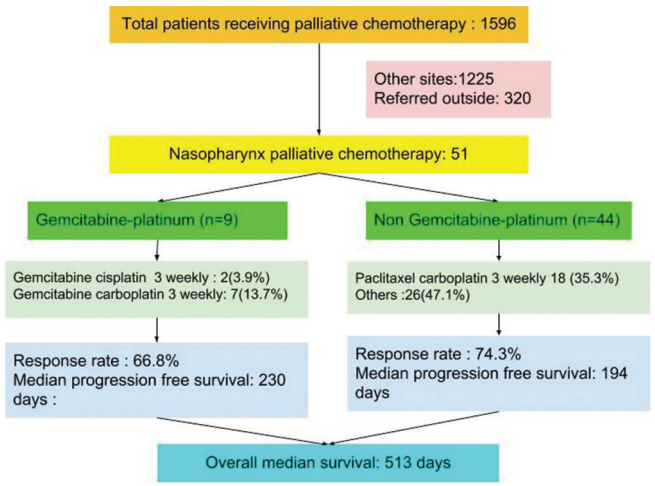

Figure 1: Flow diagram depicting treatment and outcomes. All percentages are with n = 51

Outcomes

At a median follow-up of 319 days, progression was seen in 28 (54.9%) patients. The median PFS was 225 days (95% CI: 164–274 days) [Figure 2]. The median PFS in patients receiving gemcitabine-platinum was 230 days (95% CI: 60–NA) versus 194 days (95% CI: 143–274) in patients receiving other regimens (P = 0.385). The median PFS in patients receiving paclitaxel-platinum was 204 days (95% CI: 127–248) versus 230 days (95% CI: 164–NA) in patients receiving other regimens (P = 0.203). The median OS was 513 days (95% CI: 286–931 days) [Figure 3]. The results of multivariate analysis for OS are shown in Table 3.

Quality of Life without Symptom and Toxicity and threshold utility analysis

Partitioned OS curve showing the three health states is shown in Figure 4. The restricted mean TOX state duration was 2.6 days (95% CI: 0.3–4.9), restricted mean TWiST duration was 219.2 days (95% CI: 184.0–254.4), and restricted mean REL duration was 74.3 days (95% CI: 38.1–110.4). The mean QTWiST duration for variable values of utility coefficients is shown in Table 4.

Table 1: Regimens used for palliation in first-line therapy

Regimen	n (%)
Paclitaxel carboplatin 3 weekly	18 (35.3)
Paclitaxel carboplatin weekly	2 (3.9)
Paclitaxel cisplatin 3 weekly	3 (5.9)
Gemcitabine cisplatin 3 weekly	2 (3.9)
Gemcitabine carboplatin 3 weekly	7 (13.7)
Docetaxel cisplatin 3 weekly	3 (5.9)
Docetaxel carboplatin 3 weekly	1 (2.0)
Paclitaxel cetuximab	4 (7.8)
Oral metronomic (methotrexate weekly 15 mg/m^2 + celecoxib 200 mg twice daily)	6 (11.8)
Single-agent gemcitabine	1 (2.0)
Ifosfamide + 5FU	1 (2.0)
Paclitaxel, ifosfamide, cisplatin	2 (3.9)
Nanoxel carboplatin	1 (2.0)

5FU=5 fluorouracil

Table 2: Toxicity associated with chemotherapy

Toxicity	n (%)
Grade 3-4 hematological	12 (23.6)
Grade 3-4 mucositis	4 (7.8)
Grade 3-4 loose motions	3 (5.9)
Grade 3-4 sensory neuropathy	1 (1.9)
Median number of cycles (IQR)	6 (4-6)
Reason for stoppage	
Ongoing	5 (9.8)
Completed course	25 (49.0)
Patient's choice	1 (2.0)
Toxicity	4 (7.8)
Progression	16 (10.5)

IQR=Interquartile range

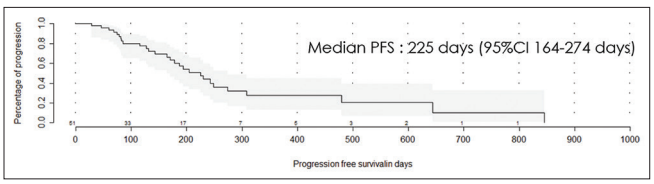

Figure 2: Overall progression-free survival curve

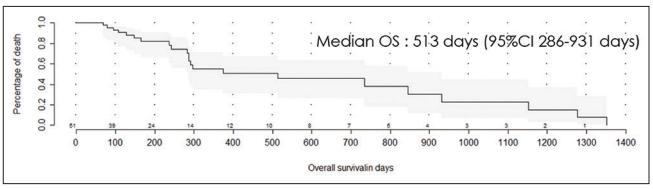

Figure 3: Overall survival curve

Second-line and beyond treatment

Only 13 patients out of 28 patients who progressed received second-line therapy (46.7%, n = 28). Only 5 patients out of 13 patients who progressed on second line received third-line therapy (55.6%).

Discussion

Locally advanced nasopharyngeal carcinomas are treated with chemotherapy and radiation.[24] When treated with two-dimensional radiotherapy techniques, locoregional failure is the commonest type of failure seen.[5] However, with the advent of intensity-modulated radiotherapy (IMRT), this is no longer true. The pattern of failure post-IMRT is distant failure. In an analysis of post-IMRT failure by Sun *et al*., distant metastasis was seen in 67.7% of patients, while locoregional failure was seen in 32.3% of patients.[25] Further, 49.4% of locoregional failures are seen within 2 years,[26] excluding salvage surgery and re-irradiation as a local therapy option. Thus, nearly 70%–80% of failures post-IMRT with chemotherapy are candidates for only systemic therapy. This signifies the importance of systemic therapy as a treatment option in recurrent, relapsed, and metastatic nasopharyngeal cancer. Similar patterns of patients were seen in our audit too. Metastatic patients contributed 51.0% of our patients. Among 49.0% who had locoregional failures, the median time to failure was 8.0 months.

The benefit of systemic cytotoxic therapy in nasopharyngeal cancer has never been proven in a randomized study. However, historical series reporting natural history confirm the fatal nature of this disease within 1 year, when untreated.[27] The multidrug combination therapies provide higher side effects without any apparent improvement in outcomes. Multiple regimens are used in literature and hence in our series too, multiple regimens were used.[16] Nearly half of our patients were exposed to platinum and one-third were exposed to taxanes and this contributed to the differential selection of regimens, in a bid to select noncross-resistant drugs. Recently, in 2016, Zhang *et al*. published the first randomized study on the selection of appropriate systemic regimen. Gemcitabine with cisplatin (GC) was the regimen associated with superior outcomes.[17] Since the publication of these results, we have started using the combination of gemcitabine-platinum as our first-line therapy. In our series, this regimen was associated with numerically higher PFS. The median PFS and OS of our study are comparable to those reported in literature.

Clinical trials often describe a plethora of toxicities, even if they might not be related to chemotherapy.[28,29] In our study too, Grade 3–4 hematological toxicity was seen in nearly one-fourth of our patients. This is similar to the hematological toxicity reported by Zhang *et al*.[17] However, the duration of toxicities in our study was short. The QTWiST analysis confirmed the short mean duration of TOX state and the minimal impact it had on the patient's QTWiST scores.

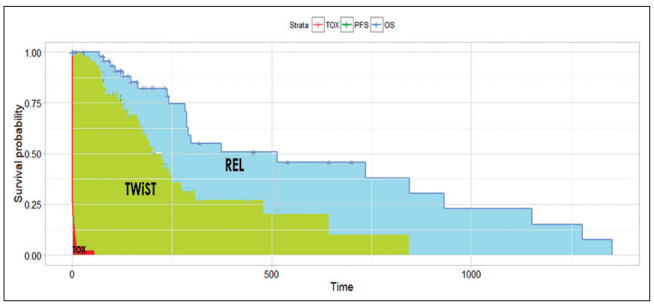

Figure 4: Partitioned overall survival curve, showing the time duration spent in TOX, TWiST, and REL states

Table 3: Result of multivariate analysis for progression-free survival and overall survival

Variable	HR	95% CI HR	*P*
Progression-free survival			
Age	0.998	0.973-1.023	0.850
ECOG PS	0.555	0.131-2.342	0.423
Indication for systemic therapy	2.263	0.921-5.561	0.075
Exposure to platinum	0.832	0.305-2.270	0.720
Recipient of gemcitabine-platinum	0.556	0.106-2.919	0.488
Recipient of paclitaxel carboplatin	1.192	0.412-3.453	0.746
Previous treatment	2.734	0.676-11.060	0.158
Overall survival			
Age	1.025	0.997-1.054	0.084
ECOG PS	0.462	0.106-2.007	0.303
Indication for systemic therapy	0.309	0.069-1.386	0.125
Exposure to platinum	1.171	0.307-4.475	0.817
Recipient of gemcitabine-platinum	0.000	0->100	0.976
Recipient of paclitaxel-carboplatin	2.894	0.841-9.965	0.092
Previous treatment	1.173	0.336-4.090	0.802

CI=Confidence interval, HR=Hazard ratio, ECOG PS=Eastern Cooperative Oncology Group performance status

Table 4: The results of threshold utility analysis

Utilities			Mean Q-TWiST in days (95% CI)
TOX	TWiST	REL	
0	1	0	219.201 (185.832-252.570)
0.25	1	0	219.853 (183.564-256.142)
0.5	1	0	220.505 (183.996-257.014)
0.75	1	0	221.157 (185.516-256.798)
1	1	0	221.809 (185.686-257.932)
0	1	0.25	237.764 (208.578-266.950)
0.25	1	0.25	238.416 (207.526-269.306)
0.5	1	0.25	239.068 (208.872-269.264)
0.75	1	0.25	239.720 (209.085-270.355)
1	1	0.25	240.372 (210.950-269.794)
0	1	0.5	256.327 (228.832-283.822)
0.25	1	0.5	256.979 (230.835-283.123)
0.5	1	0.5	257.631 (229.732-285.530)
0.75	1	0.5	258.283 (229.679-286.887)
1	1	0.5	258.935 (231.436-286.434)
0	1	0.75	274.890 (248.111-301.669)
0.25	1	0.75	275.542 (246.806-304.278)
0.5	1	0.75	276.194 (247.349-305.039)
0.75	1	0.75	276.846 (250.068-303.624)
1	1	0.75	277.498 (250.775-304.221)
0	1	1	293.453 (263.722-323.184)
0.25	1	1	294.105 (262.667-325.543)
0.5	1	1	294.757 (263.125-326.389)
0.75	1	1	295.409 (264.561-326.257)
1	1	1	296.061 (264.125-327.997)

Q-TWiST=Quality of Life without Symptom and Toxicity, CI=Confidence interval

The REL state or the duration of time between first-line progression and death was large. This signifies the importance of second-line and beyond treatment. It is interesting to note that, in the trial reported by Zhang *et al*., post GC, only 41% of patients received second-line therapy.[17] The figures were similar in our study, with second-line and third-line therapies being received by 46.7% and 55.6% of patients, respectively. Traditionally, in nasopharyngeal cancer studies, chemotherapy is given for 6 cycles in 21-day cycles and for 24 weeks in weekly cycling protocols.[17,21,30] Whether continuation of chemotherapy beyond 6 cycles in the 21-day cycle protocol would improve the outcomes is not clear from literature. We performed this analysis to study the impact of continuation of chemotherapy beyond 6 cycles (data not shown in results). However, the hazard ratio for this analysis was 0.990 (95% CI: 0.808–1.213), $P = 0.924$, clearly signifying that continuation of the same chemotherapy beyond 6 cycles was unlikely to help. Whether switch maintenance with a noncross-resistant drug regimen having negligible toxicities would improve outcomes and maintain performance status of patients is a worthwhile research question.[31]

The current analysis has its own limitations. It was a single-center, retrospective study, and a number of regimens were used. However, the study provides the real-world scenario of systemic treatment of nasopharyngeal cancers.

Conclusion

Systemic cytotoxic therapy in nasopharyngeal cancers is associated with high response rates with low duration of time spent in adverse events. GC regimen provides numerically higher PFS over paclitaxel and carboplatin. Continuation of chemotherapy beyond 6 cycles is unlikely to be helpful in improving PFS. A high REL state is seen in this cancer, signifying the importance of administering second-line and beyond chemotherapies in patients who are fit for the same.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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