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ORIGINAL RESEARCH

Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma by Targeting the Epidermal Growth Factor Receptor Combined with Gemcitabine Plus Platinum

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Purpose: The purpose of this study was to evaluate the anti-tumor activity and safety of anti-epidermal growth factor receptor (EGFR) monoclonal antibody combined with gemcitabine plus platinum (GP) as a first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (RM-NPC).

Patients and Methods: This retrospective study analyzed RM-NPC patients at Sun Yat-sen University Cancer Center who received anti-EGFR antibody plus GP as a first-line treatment between July 2007 and November 2018. Survival analyses were performed using the Kaplan–Meier method with Log rank test. Cox proportional hazards model was used for the multivariate analysis.

Results: A total of 84 patients were enrolled. The median progression-free survival (PFS) was 10.3 months (95% CI, 6.9–13.6 months), and the median overall survival (OS) was 42.8 months (95% CI, 24.6–60.9 months). The objective response rate and disease control rate were 67.9% and 92.9%, respectively. The multivariate analysis identified a higher baseline EBV DNA level as a risk factor for both PFS (P=0.025) and OS (P=0.013). Additionally, age≥44 years (P =0.003), non-cisplatin (P= 0.009), and poor KPS (≤80) (P =0.034) were other risk factors for OS. The most common adverse events were leukopenia (n=73, 86.9%). The most common grade 3–4 AEs were leukopenia (n=30, 35.7%) and thrombocytopenia (n=22, 26.2%).

Conclusion: Anti-EGFR monoclonal antibody plus GP achieved promising antitumor activity with a tolerable toxicity profile in RM-NPC as a first-line treatment. Randomized clinical trials are warranted to compare the efficacy of GP with or without anti-EGFR antibody in these patients.

Keywords: advanced cancer, chemotherapy, oncology, targeted therapy

Introduction

The distribution of nasopharyngeal carcinoma (NPC) is extremely unbalanced, with more than 70% new cases in east and southeast Asia. Intensity modulated radiation therapy (IMRT) and platinum-based combined chemotherapy have substantially improved local regional disease control.[1] However, approximately 10% of NPC patients experience recurrence and 11–36% of patients have distant metastases.[2] Recurrent or metastatic NPC (RM-NPC) patients have a very poor median survival (range: 15 to 30 months) due to therapeutic resistance and intolerance.[3] Gemcitabine

plus cisplatin was established as a first-line chemotherapy for RM-NPC based on the reported findings of a randomized Phase III clinical trial.[4]

Several solid tumors overexpress epidermal growth factor receptor (EGFR), suggesting that it may represent an important prospective therapeutic target for several types of cancer.[5] Monoclonal antibodies (mAbs) for anti-EGFR can activate various molecular pathways associated with the regulation of cellular proliferation, differentiation, and survival by preventing tyrosine kinase phosphorylation by blocking the ligand from binding to the extracellular domain.[6,7] EGFR has also been reported to be highly expressed in over 90% NPC patients and linked to an adverse prognosis.[8,9] Therefore, anti-EGFR mAbs may represent a promising treatment for NPC.

Typically, nimotuzumab (NTZ) and cetuximab (CTX) are the most common anti-EGFR mAbs administered to treat NPC. Many reports suggest that both NTZ and CTX can enhance the effectiveness of current treatments for locoregionally advanced NPC.[10–12] However, the treatment efficacy of anti-EGFR mAbs combined with typical first-line chemotherapy in RM-NPC remains poorly understood. Therefore, we sought to elucidate the anti-tumor activity and safety profile associated with anti-EGFR mAbs combined with gemcitabine plus platinum (GP) as a first-line treatment for RM-NPC.

Patients and Methods

Patients

The records of patients with RM-NPC who were treated at the Sun Yat-sen University Cancer Center from July 2007 to November 2018 were assessed. Patients were included in the study if they met the following criteria: 1) histologically confirmed nasopharyngeal carcinoma; 2) recurrent or metastatic disease after primary standard treatment (patients who had recurrent diseases within six months after platinum treatment were excluded), or primarily metastasis; 3) without previous systemic chemotherapy for recurrent or metastatic disease; 4) received gemcitabine plus platinum as palliative chemotherapy; and 5) received at least one cycle of anti-EGFR mAbs as combination treatment. Patients with incomplete clinical data and enrolled in any clinical trials were excluded. Figure 1 illustrates the process used to select the patients.

The institutional review board of Sun Yat-sen University Cancer Center approved this retrospective study (approval number: B2019-106-01). Since this study was retrospectively designed, informed consent was waived. All patients'

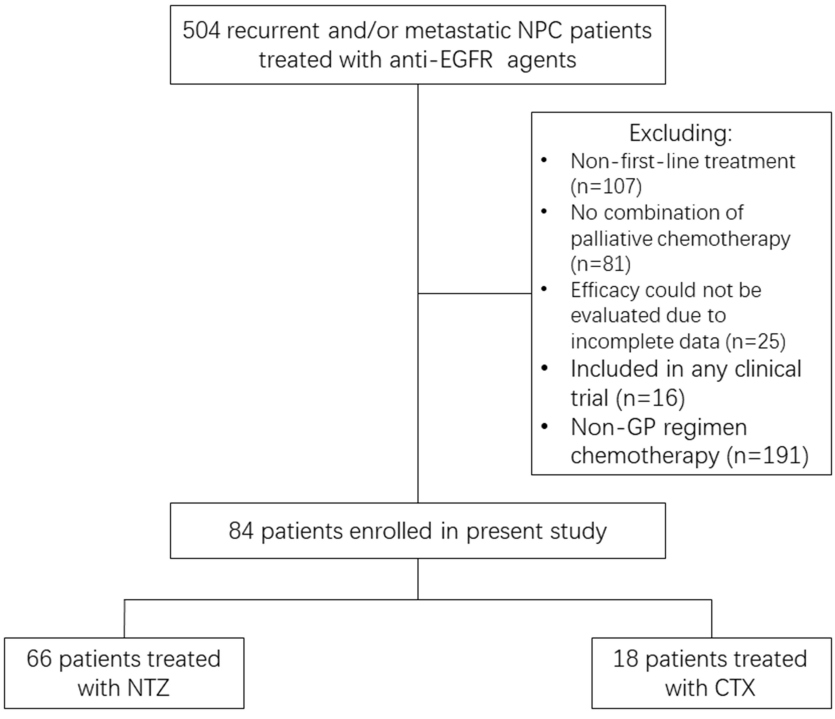

Figure 1 Diagram illustrating patients inclusion and exclusion.
Abbreviations: NPC, nasopharyngeal carcinoma; EGFR, anti-epidermal growth factor receptor; NTZ, nimotuzumab; CTX, cetuximab.

personal information and clinical data was anonymous and confidentiality. This study followed the guidelines according to the Declaration of Helsinki.

Treatment

All patients received an intravenous administration of gemcitabine (1 g/m^2 on day 1 and day 8) plus cisplatin or nedaplatin (80 mg/m^2 on day 1) as first-line palliative chemotherapy once every three weeks. For patients with impaired renal function, cisplatin or nedaplatin was replaced by carboplatin (AUC = 5 intravenously on day 1). Anti-EGFR mAbs were administered intravenously concurrent with chemotherapy. The initial dosage of cetuximab was 400 mg/m^2. A dosage of 250 mg/m^2 was used for all subsequent administrations. Nimotuzumab was administered (200 mg/m^2), weekly to triweekly. The patient records were used to extract the specific treatment regimens (medication used, dosage, mode of administration, and any modifications at the discretion of each treating physician).

Data Processing

Age was grouped according to the median value. The Karnofsky performance score (KPS)[13] was evaluated on a scale ranging from 0 to 100 (containing 10 levels) and was divided into two subsets based on a score of 80 (KPS > 80, and KPS ≤ 80). The plasma EBV DNA concentration was measured via real-time quantitative polymerase chain reaction as described previously.[14] EBV DNA was grouped according to the concentration, which was defined by magnitudes of 10. All medical imaging for evaluating treatment efficacy was independently reviewed by the first two authors. Any discrepancies were resolved by discussion. All adverse events (AEs) were documented according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0 and retrospectively extracted from the medical records.

Endpoints and Statistical Analysis

The primary endpoint in this study was progression-free survival (PFS). PFS was determined as the date from commencement of first-line treatment until disease progression or death. The overall survival (OS; the time from the commencement of first-line therapy until the date of death from any cause) and tumor response were considered secondary endpoints. The tumor response was evaluated by MRI or CT in accordance with the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 once every two cycles or at the physician's discretion, which comprised the partial response (PR), stable disease (SD), complete response (CR), and progressive disease (PD). Patients with bone metastasis alone were unevaluable and considered to be SD in cases of non-CR and non-PD, and as PD if new lesions appeared. The proportion of CR + PR constituted the objective response rate (ORR). The proportion of CR + PR + SD represented the disease control rate (DCR).

The Kaplan–Meier method was used for the survival analysis with a Log rank test. Multivariate analyses were performed using a Cox proportional hazards model with a hazard ratio (HR) and 95% confidence intervals (CIs). All statistical analyses were performed using SPSS version 21.0 (Chicago, IL, USA). A threshold of $P < 0.05$ was indicative of significance. A Sankey diagram was used to visually represent the sequential distribution flow of patients from those exhibiting the most favorable tumor response (CR, PR, SD, or PD) to progression status (progression-free or not), and the final survival state (death or not), in which the width of the branch was shown to be proportionate to the flow quantity. The Sankey diagram was implemented by R version 3.5.2 with "Networkd3" package.

Results

Demographics

The characteristics of the 84 RM-NPC patients (median age: 44 years [range: 17–72 years]) are listed in Table 1. Undifferentiated non-keratosis carcinoma was the primary histopathology (n = 75, 89.3%). Most patients were treated with NTZ as an anti-EGFR treatment (n = 66, 78.6%), whereas the remaining 18 (21.4%) patients were treated with CTX. For the course of chemotherapy, 17 patients received less than 4 cycles, 28 patients received 4 or 5 cycles, and 39 patients received 6 or more cycles. Among the 32 recurrent patients, 19 patients were classified as recurrence alone and 13 patients had recurrence with metastasis. The lung was the most common metastatic site (n = 33, 39.3%) followed by bone metastasis (n = 30, 35.7%).

Survival Analysis

The last follow-up date was August 16, 2019, with an 18.9-month median follow-up time (interquartile range: 11.8–38.3 months). Following first-line GP treatment combined with anti-EGFR mAbs, 50 (59.5%) patients experienced progression and 23 (27.4%) patients died before the data cut-off date (survival curves are provided in Figure 2A

Table 1 The Baseline Characteristics of Patients

Characters	Patients (%)
Gender	
Male	66 (78.6)
Female	18 (21.4)
Age	
< 44y	39 (46.4)
≥ 44y	45 (53.6)
Smoke	
Yes	22 (26.2)
No	62 (73.8)
Anti-EGFR agent	
Nimotuzumab	66 (78.6)
Cetuximab	18 (21.4)
Type of platinum	
Cisplatin	60 (71.4)
Carboplatin	14 (16.7)
Nedaplatin	10 (11.9)
Pathological histology	
Undifferentiated non-keratosis	75 (89.3)
Others[a]	9 (10.7)
Recurrence/Metastasis sequence[b]	
Synchronous Metastasis	10 (11.9)
Metachronous	
Metachronous Metastasis	42 (50.0)
Recurrence	19 (22.6)
Recurrence with Metastasis	13 (15.5)
Sites of metastasis	
Lung	33 (39.3)
Liver	21 (25.0)
Bone	30 (35.7)
Others	28 (33.3)
Karnofsky Performance Score (KPS)	
> 80	65 (77.4)
≤ 80	19 (22.6)
Baseline Epstein-Barr virus DNA level (copies/mL)	
<10E3	23 (27.4)
≥10E3 and <10E4	26 (30.9)
≥10E4 and <10E5	22 (26.2)
≥10E5	13 (15.5)

Notes: [a]Other pathological histology types contained non-keratosis, differentiated non-keratosis, squamous carcinoma, and unknown type. [b]Synchronous Metastasis: distant metastasis at initial diagnosis; Metachronous Metastasis: experience distant metastasis more than 6 months after radical treatment; Recurrence: relapse in nasopharynx or regional lymph nodes of neck more than 6 months after radical treatment; Recurrence with Metastasis: experience both locoregional recurrence and distant metastasis more than 6 months after radical treatment

Abbreviation: EGFR, epidermal growth factor receptor.

and B). The median PFS of the patients was 10.3 months (95% CI: 6.9–13.6 months) and median OS was 42.8 months (95% CI: 24.6–60.9 months).

Regarding the best tumor response, 4 (4.8%) patients achieved CR, 53 (63.1%) patients had PR, 21 (25.0%) had SD, and 6 (7.1%) had PD, respectively. The ORR was 67.9% and DCR was 92.9%. The most favorable changes in the total longest target lesion diameter from baseline for each patient are shown in Figure 2C. The sequential distribution flow of patients from the best tumor response to final survival is presented in Figure 2D.

Prognostic Analysis

Table 2 lists the univariate and multivariate analyses of the PFS and OS. In the PFS univariate analysis, only the baseline EBV DNA level (P = 0.022) was identified as significant factor. After adjusting for gender and age in the multivariate analysis, the baseline EBV DNA level remained an independent prognostic factor (P = 0.025, HRs listed in Table 2) for PFS.

For OS, the univariate analysis revealed that KPS (P = 0.017), type of platinum (P = 0.006) and baseline EBV DNA level (P = 0.007) were significant prognostic factors. The recurrence/metastasis sequence (P = 0.050) had potential effect on the OS. Four independent risk factors were finally identified by multivariate analysis, including age ≥44 years (P = 0.003), non-cisplatin (P = 0.009), poor KPS (≤80) (P = 0.034), and a higher baseline level of EBV DNA (P = 0.013). The HRs of the above prognostic factors are presented in Table 2.

Safety Analysis

The detailed AEs are presented in Table 3. There were 80 patients (95.2%) who had at least one adverse event with any grade. The most common AEs were leukopenia (n = 73, 86.9%), thrombocytopenia (n = 50, 59.5%), and decreased appetite (n = 50, 59.5%), followed by nausea (n = 39, 46.4%). One-third of the patients suffered from liver function damage, including an elevation in alanine aminotransferase (ALT) in 31.0% (n = 26) patients and an aspartate aminotransferase (AST) elevation in 29.8% (n = 25) patients. Only one quarter of the patients vomited (n = 21, 25%). The most frequently occurring grade 3–4 AEs were leukopenia (n = 30, 35.7%) and thrombocytopenia (n = 22, 26.2%). The presence of a rash often occurred in

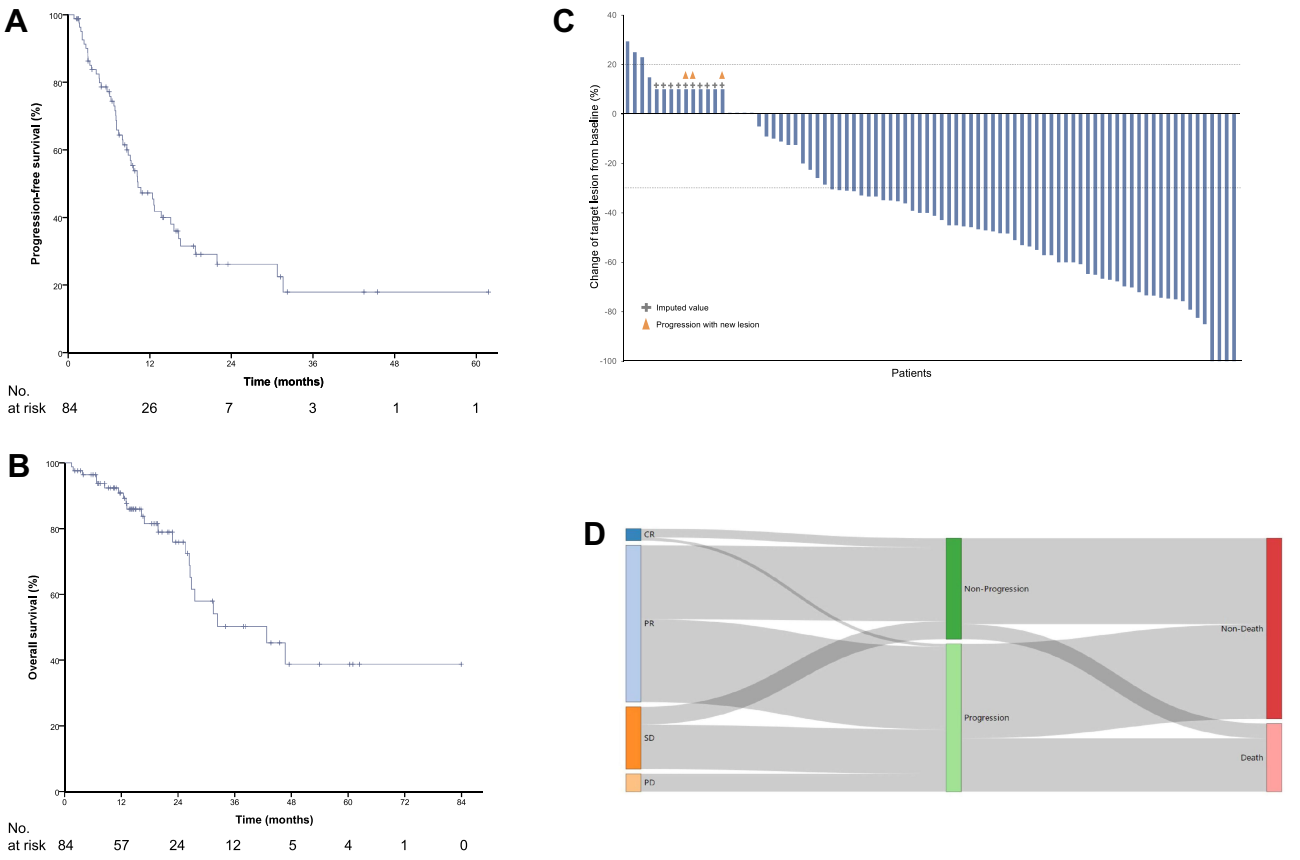

Figure 2 Survival curves and tumor response. (**A**) progression-free survival curve; (**B**) overall survival curve. (**C**) Best changes from baseline in sum of longest target lesion diameter per patient. Imputed value was used for patients with bone metastasis alone, who were unevaluable and were given a 10% value. Progression with new lesion was marked for patients who progressed with new lesion but had shrinkage in the sum of longest target lesion. (**D**) Sequential distribution flow of patients from best tumor response to final survival. In CR subset, 75% (n=3) patients were progression free, and 25% (n=1) patients were progression. In PR subset, 47.2% (n=25) patients were progression free and 52.8% (n=28) patients were progression. In SD subset, 28.6% (n=6) patients were progression free and 71.4% (n=15) were progression. All patients (n=6) in PD subset had progression. Among non-progression patients, 85.3% (n=29) were alive (non-death) and 14.7% (n=5) were death. Among progression patients, 64% (n=32) were alive (non-death) and 36% (n=18) were death.

patients treated with CTX (6 of 18, 33.3%) compared with those treated with NTZ (5 of 66, 7.6%).

Discussion

Our results indicate that combined therapy with anti-EGFR mAbs plus GP achieved encouraging PFS, OS, and response rate, with an acceptable level of toxicity as first-line RM-NPC treatment. Moreover, gemcitabine plus cisplatin represents the gold-standard first-line systemic therapy for RM-NPC, since gemcitabine plus cisplatin achieved a longer PFS than fluorouracil plus cisplatin (FP) (median 7.0 vs. 5.6 months, respectively) in a randomized phase III clinical trial.[4] The response rate for gemcitabine plus cisplatin was also higher than that of FP (64% vs. 42%, respectively; $P < 0.001$). Despite statistical differences, mild clinical improvement indicates that there is a limitation that affects the treatment efficacy of chemotherapy alone. This may be related to platinum-resistant tumor clones harbored in RM-NPC, which may be associated with activation of the EGFR signaling pathway.[15,16] Thus, blocking the EGFR pathway using anti-EGFR mAbs could resensitize these cancer cells to chemotherapy and improve the associated curative effect.

Recently, this hypothesis has been tested in a Phase II clinical trial by Zhao et al[17] that enrolled 35 RM-NPC patients. However, the small patient sample received an FP regimen as chemotherapy, which is not the gold-standard first-line therapy. Moreover, the median PFS, ORR, and median OS were 7 months, 71.4%, and 16.3 months, respectively when nimotuzumab was added to FP. This comparable survival and tumor response with gemcitabine plus cisplatin suggest that anti-EGFR therapy might increase the efficacy of chemotherapy and delay disease progression.

Table 2 Univariate and Multivariate Analyses of Progression-Free Survival and Overall Survival

Characters	Progression-Free Survival			Overall Survival		
	P-Uni	P-Multi	HR (95% CI)	P-Uni	P-Multi	HR (95% CI)
Gender						
Male	0.849	0.732	1	0.969	0.806	1
Female			1.133 (0.556–2.309)			1.145 (0.388–3.383)
Age						
< 44y	0.465	0.310	1	0.106	0.003	1
≥ 44y			1.362 (0.751–2.470)			6.643 (1.929–22.875)
Smoke						
Yes	0.270	NA	NA	0.840	NA	NA
No						
Anti-EGFR agent						
Nimotuzumab	0.714	NA	NA	0.980	NA	NA
Cetuximab						
Type of platinum						
Cisplatin	0.319	NA	NA	0.006	0.009	1
Carboplatin						2.262 (0.717–7.139)
Nedaplatin						11.719 (2.408–57.038)
Pathological histology						
Undifferentiated non-keratosis	0.148	NA	NA	0.465	NA	NA
Others[a]						
Recurrence/Metastasis sequence[b]						
Synchronous Metastasis	0.135	NA	NA	0.050	0.186	1
Metachronous Metastasis						1.708 (0.196–14.883)
Recurrence						0.640 (0.043–9.460)
Recurrence with Metastasis						5.111 (0.507–51.535)
Karnofsky Performance Score (KPS)						
> 80	0.972	NA	NA	0.017	0.034	1
≤ 80						3.135 (1.092–8.998)
Baseline Epstein-Barr virus DNA level (copies/mL)						
<10E3	0.022	0.025	1	0.007	0.013	1
≥10E3 and <10E4			1.532 (0.655–3.583)			1.127 (0.228–5.583)
≥10E4 and <10E5			3.172 (1.395–7.215)			3.133 (0.599–16.382)
≥10E5			2.657 (1.036–6.817)			8.384 (1.767–39.785)

Notes: [a]Other pathological histology types contained non-keratosis, differentiated non-keratosis, squamous carcinoma, and unknown type. [b]Synchronous Metastasis: distant metastasis at initial diagnosis; Metachronous Metastasis: experience distant metastasis more than 6 months after radical treatment; Recurrence: relapse in nasopharynx or regional lymph nodes of neck more than 6 months after radical treatment; Recurrence with Metastasis: experience both locoregional recurrence and distant metastasis more than 6 months after radical treatment.

Abbreviations: EGFR, epidermal growth factor receptor; P-uni, P value for univariate analysis; P-multi, P value for multivariate analysis; HR, hazard ratio; CI, confidence interval.

Several prognostic factors were separately identified for the PFS and OS in our study. As an important prognostic factor for NPC,[18] baseline EBV-DNA was positively correlated with the PFS and OS risk in RM-NPC. In particular, there was a substantial increase in the overall survival risk as the level of EBV DNA increased. Age ≥44y and KPS ≤ 80 were risk factors for OS. Age represents a common influencing factor on the survival outcomes of a variety of metastatic cancers, including metastatic NPC.[19] This may be attributed to a poor treatment tolerance among elderly patients or limited performance. The poor OS of patients who did not receive non-cisplatin chemotherapy might be related to the fact that patients with renal damage are more likely to select carboplatin. Similarly, patients who

Table 3 Common Treatment-Related Adverse Events

Adverse events	No (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3+4 (%)	All Grade (%)
Leukopenia	11 (13.1)	10 (11.9)	33 (39.3)	22 (26.2)	8 (9.5)	30 (35.7)	73 (86.9)
Thrombocytopenia	34 (40.5)	13 (15.5)	15 (17.9)	9 (10.7)	13 (15.5)	22 (26.2)	50 (59.5)
Vomiting	63 (75.0)	16 (19.0)	5 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (25.0)
Nausea	45 (53.6)	32 (38.1)	7 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	39 (46.4)
Mucosal inflammation	79 (94.0)	4 (4.8)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.0)
Decreased appetite	34 (40.5)	43 (51.2)	7 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	50 (59.5)
Diarrhea	81 (96.4)	2 (2.4)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.6)
Nephrotoxicity	63 (75.0)	20 (23.8)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	21 (25.0)
Hypotension	71 (84.5)	13 (15.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (15.5)
Weight loss	62 (73.8)	20 (23.8)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	22 (26.2)
Rash	73 (86.9)	11 (13.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (13.1)
Fever	67 (79.8)	15 (17.9)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	17 (20.2)
ALT elevation	58 (69.0)	23 (27.4)	2 (2.4)	1 (1.2)	0 (0.0)	1 (1.2)	26 (31.0)
AST elevation	59 (70.2)	24 (28.6)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	25 (29.8)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

experience serious gastrointestinal side effects have an increased tendency to select nedaplatin.

Most AEs in this study were well tolerated and manageable, and primarily attributed to chemotherapy. The proportion of grade 3–4 leukopenia and any grade of vomiting were both lower than that described by Zhao et al,[17] which may be related to the recent use of PEG-rhG-CSF and more standardized antiemetic therapy. Mild fever and rash were reported, which was related to the drug properties associated with mAbs.[20]

The limitations of our study are related to its retrospective nature, which may bias the results. In an attempt to overcome this deficiency, we performed a multivariate analysis to any reduce confounding effects. Second, we lacked EGFR expression information, associated with various technical issues related to the tissue samples and challenges in conducting vigorous inter-laboratory quality control of EGFR expression. Third, treatment information and adverse events were retrospectively collected from clinical medical records. Due to these issues, this study did not aim to determine the optimal drug dosage, and adverse events might also be underreported. Fourth, the short follow-up period of this study led to the instability of the median OS. Finally, this study did not assess the efficacy between anti-EGFR mAbs plus chemotherapy compared to chemotherapy alone. While this retrospective study did not aim to establish a new standard of care, the preliminary anti-tumor activity and safety data provides insight for future confirmatory prospective studies.

In addition, it is important to mention that immunotherapy has increasingly been tested as a treatment for advanced tumors, including RM-NPC.[21–23] The KEYNOTE-028[21] Study and NCI-9742 studies[22] demonstrated promising antitumor activity of single agent of pembrolizumab and nivolumab, respectively, in patients with RM-NPC, as the second or more line therapy. The same result was also documented for camrelizumab (SHR-1210).[23] Moreover, in the Phase I trial of SHR-1210,[23] the combination of camrelizumab plus gemcitabine and cisplatin achieved a promising preliminary antitumor activity for treatment-naive RM-NPC patients. On the basis of these findings, whether the combined targeted therapy (eg, anti-EGFR) could achieve more exciting curative effects is worthy of further exploration.

Conclusion

Anti-EGFR mAbs combined with GP achieved promising anti-tumor response with a limited toxicity profile as a first-line treatment for RM-NPC. Future studies are required to confirm the safety and efficacy of anti-EGFR mAbs plus GP compared to GP alone for RM-NPC treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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