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Palliative systemic therapy for recurrent or metastatic nasopharyngeal carcinoma – How far have we achieved?

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is endemic in Southern China, Taiwan, Malaysia, Singapore, North Africa and Alaska. About 30% of NPC patients develop recurrence or metastasis despite initial radical treatment. Palliative chemotherapy is the first-line treatment for inoperable recurrence or distant metastatic disease. However the standard first-line chemotherapeutic regimen is yet to be established until recently gemcitabine and cisplatin has been proven superior to traditional regimen with 5-FU and cisplatin shown in a phase III randomized-controlled trial. Further palliative systemic treatment options including other chemotherapeutic regimens, targeted therapy and more recently immunotherapy have gradually evolved. We provided a comprehensive review on different traditional chemotherapeutic regimens and highlighted the latest chemotherapeutic treatments as well as the latest development of targeted therapies, immune checkpoint inhibitors and other immunotherapeutic options in this setting.

1. Introduction and epidemiology

Nasopharyngeal carcinoma is distinctive in terms of geographical distribution and the histology. It is an endemic malignancy in Southern China, followed by Taiwan, Malaysia, Singapore, North Africa and Alaska, with a peak incidence of 30 per 100,000 persons (Jia et al., 2006; Parkin et al., 2005). The undifferentiated type (WHO Type III), strongly associated with Epstein-Barr virus (EBV) infection, is the most common histological type in the endemic areas whereas squamous cell type (WHO Type I) is the predominant type in the low-incident regions. Radiotherapy with contemporary techniques like intensity-modulated radiation therapy (IMRT) is the mainstay of treatment for early stage NPC, while concurrent chemoradiation with or without adjunct chemotherapy is indicated for locoregionally advanced disease, as shown in the first meta-analysis in 2006 and a recent update in 2015 with inclu-

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Table 1
Single-agent chemotherapy in recurrent and/or metastatic nasopharyngeal carcinoma as first-line and/or subsequent line setting.

Study	Setting	Phase	Number of Patients	Regimen	OR Rate (%)	CR Rate (%)	Median PFS	Median OS
1st line or beyond								
Foo	1st line or beyond	Phase II	25 M pretreated 27 M untreated	G	28 48	4 3.7	3.6 months 5.1 months	7.2 months 10.5 months
Ma	1st line or beyond	Retrospective	18 R + M	G	34	6	31% (1-month)	48% (1-year)
2nd line or beyond								
Dugan	2nd line or beyond	Phase II	108 R + M	MIT	25	NR	4.5 months	13 months
Au	2nd line or beyond	Phase II	24 M	PAC	21.7	0	7.5 months	12 months
Poon	2nd line or beyond	Phase II	28 M	IRI	14	0	3.9 months	11.4 months
Chua	2nd line	Phase II	17 R + M	CAP	23.5	5.9	4.9 months	7.6 months
Chua	2nd line or beyond	Retrospective	49 R + M	CAP	37	6	5 months	14 months; 54% (1-year)
Ciuleanu	2nd line or beyond	Phase II	26 R + M	CAP	48	9	14 months	62% (1-year)
Zhang	2nd line or beyond	Phase II	32 R + M	G	43.8	0	5.1 months	16 months; 63% (1-year)
Ngeow	2nd line or beyond	Phase II	30 R + M	DOC (weekly)	37	0	5.3 months	12.8 months
Zhang	2nd line or beyond	Phase II	35 R + M	PEM	2.9	0	1.5 months	13.3 months
Peng	2nd line or beyond	Retrospective	39 R + M	S-1	30.7	2.6	5.6 months (median TTP)	13.9 months
Tsao	2nd line	Phase II	13 M	TAS-106	0	0	48 days	280 days
Lee	3rd line or beyond	Phase II	11 R 45 M	CYC	8.9	0	9.0 months 4.1 months	14.5 months 8.4 months

CAP = capecitabine, CR = complete response, CYC = cyclophosphamide, DOC = docetaxel, G = gemcitabine, IRI = irinotecan, M = metastatic, MIT = mitoxantrone, NR = not reported, OR = objective response, OS = overall survival, PAC = paclitaxel, PEM = pemetrexed, PFS = progression-free survival, R = recurrent, TTP = time to progression.

sion of 19 trials and 4806 patients (Baujat et al., 2006; Blanchard et al., 2015). Nevertheless, about 30% of cases relapse locoregionally or distantly, despite intensive definitive treatment (Lee et al., 2005). Though most of these relapsed patients have an unfavorable survival outcome, their survival can be significantly prolonged with palliative chemotherapy and more recently targeted therapy has demonstrated encouraging objective responses and treatment outcomes. In this review, we comprehensively presented the treatment outcomes of the previous studies on palliative chemotherapy, targeted therapy, immunotherapy and the future directions on the use of novel treatments for recurrent or metastatic NPC.

2. Palliative chemotherapy

Systemic chemotherapy has been the mainstay of first-line treatment for incurable recurrent or metastatic NPC. For the past 30 years, trials investigating the efficacy and safety were all retrospective or small-scale phase II clinical trials and there have been few phase III randomized-controlled trials comparing efficacy and safety of different chemotherapeutic regimens and no evidence pertaining to prolongation of survival compared to best supportive care. Moreover, these trials consisted of a heterogeneous population treated in different settings (first-line, second-line or beyond). In addition, quality-of-life evaluations before and after chemotherapy were often neglected. Instead of summarizing the published trials treated in different lines of settings, we now described their treatment outcomes according to the number of chemotherapeutic agents used, namely monotherapy, doublet combination chemotherapy and polychemotherapy.

2.1. Single-agent chemotherapy

Anecdotal publications consisting mainly of retrospective studies have demonstrated that the use of old agents like methotrexate, bleomycin, 5-fluorouracil (5-FU), epidoxorubicin, mitoxantrone, and platinum compounds produced an objective response rates between 15 and 30% (Shiu and Tsao 1989; Dugan et al., 1993; Ma and Chan 2005). More recent clinical trials have also investigated the efficacy of newer agents including gemcitabine, irinotecan, paclitaxel, capecitabine, and docetaxel (Table 1) (Dugan et al., 1993; Au et al., 1998; Foo et al., 2002; Ma et al., 2002; Chua et al., 2003; Poon et al., 2005; Chua et al., 2008a,b; Ciuleanu et al., 2008; Zhang et al., 2008; Ngeow et al., 2011). Notably, gemcitabine and capecitabine are the foci of recent studies, offering an objective response rates between 24 and 48% and median progression-free survival (PFS) between 4 and 14 months (Foo et al., 2002; Ma et al., 2002; Chua et al., 2003; Chua et al., 2008a,b; Ciuleanu et al., 2008; Zhang et al., 2008). Docetaxel, as a single agent, also produced a response rate of 37% and a median PFS of 5 months (Ngeow et al., 2011).

There has been no standard third-line treatment or beyond as the performance status of these patients gradually decline brought by the side effects attributed to the use of prior first-line and second-line treatment. Lee et al. has recently published the use of metronomic oral cyclophosphamide as third-line treatment or beyond for recurrent/metastatic disease (Lee et al., 2017). Metronomic oral chemotherapy may provide an ideal choice to patients treated in this setting by shifting the targets from tumor cells to tumor vasculature so as to reduce the chance of drug resistance as well as offering a relatively low toxicity profile to them who have been significantly jeopardized by the long-term complica-