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REVIEW ARTICLE **CME**

Palliative Chemotherapy and Targeted Therapy for Recurrent and Metastatic Nasopharyngeal Carcinoma: Reminiscences and the Future

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ABSTRACT

Nasopharyngeal carcinoma of undifferentiated type is an endemic cancer with a high incidence in Southern China, Taiwan, and Singapore, followed by North African countries and Alaska. Despite intensive definitive treatment, regrettably about 30% of patients still suffer from loco-regional relapse or even distant metastasis. Palliative chemotherapy has been the standard treatment for those whose disease is not amenable to further radical surgery or a second course of radiotherapy. Though mainly given with palliative intent, this form of chemotherapy can achieve excellent symptom control and prolong survival. More recently targeted therapy has also been widely evaluated in metastatic nasopharyngeal carcinoma. Here we provide a comprehensive review on the use of various types of palliative chemotherapy and targeted therapy for recurrent and metastatic nasopharyngeal carcinoma by searching the MEDLINE and PubMed databases from 1980 to March 2013. The key words used were "nasopharyngeal", "nasopharynx", "recurrent", "metastatic", "chemotherapy", "targeted therapy", and "immunotherapy".

Key Words: *Antineoplastic agents; Carcinoma; Nasopharyngeal neoplasms; Neoplasm recurrence, local; Radiotherapy, adjuvant*

中文摘要

復發性和轉移性鼻咽癌的姑息性化療和靶向治療：回顧與前瞻

李浩勳、鄺麗雲

未分化型鼻咽癌是一種地方性癌症，在中國南部、台灣和新加坡的發病率偏高，其次為北非國家和阿拉斯加。儘管施以針對性強化治療，仍然有約30%的患者遭受癌症局部復發甚至遠處轉移的痛苦。對於那些不適合接受擴大根治性手術或第二療程放療的患者來說，姑息性化療一向是標準的治療方法。雖然該形式的化療主要以姑息緩解為目的，卻可達到出色的症狀控制並延長生存期。最近，以靶向治療醫治轉移性鼻咽癌被廣泛評估。我們檢索MEDLINE和PubMed數據庫中1980年至2013年3月的相關文獻，全面回顧復發性和轉移性鼻咽癌的各種類型姑息性化療和靶向治療的運用。使用的關鍵字為「鼻咽癌」（nasopharyngeal），「鼻咽部」（nasopharynx），「復發」（recurrent），「轉移」（metastatic），「化療」（chemotherapy），「靶向治療」（targeted therapy）和「免疫治療」（immunotherapy）。

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INTRODUCTION

Undifferentiated nasopharyngeal carcinoma (NPC) is an endemic cancer with a high incidence in Southern China, Taiwan, and Singapore, and a lower incidence in North African countries and Alaska. Radiotherapy is the mainstay of treatment for early stage NPC, while concurrent chemoradiation is indicated for locoregionally advanced disease, as revealed by previous phase III randomised controlled trials and a recent meta-analysis.[1] Nevertheless, about 30% of cases relapse locoregionally or distantly, despite intensive definitive treatment.[2] Though most of these relapsed patients have an unfavourable 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 article, we comprehensively review the previous literature on the use of palliative chemotherapy and comment on the use of targeted therapy and other novel future treatments for recurrent and metastatic NPC.

METHODS

MEDLINE and PubMed databases were searched from 1980 till March 2013. Key words including "nasopharyngeal", "nasopharynx", "recurrent", "metastatic", "chemotherapy", "targeted therapy", and "immunotherapy" were used for the literature search.

PALLIATIVE CHEMOTHERAPY

Although well established as a standard treatment for metastatic NPC, there have been no randomised trials comparing efficacy of different chemotherapeutic regimens and no evidence pertaining to prolongation of survival compared to best supportive care.[3] Apart from that, quality-of-life assessment during chemotherapy is often ignored in these retrospective or phase II studies. Moreover, the majority are small-scale studies that are inherently difficult for the purpose of meaningful comparison between different chemotherapy regimens. In summary, these trials can be categorised into monotherapy, doublet chemotherapy, and polychemotherapy studies used in chemo-naïve patients or those who have received prior chemotherapy for recurrent / metastatic disease.

Monotherapy

Anecdotal reports have demonstrated that the use of older agents like methotrexate, bleomycin, 5-fluorouracil (5-FU), epidoxorubicin, mitoxantrone, and platinum compounds produce a response rate between 15 and 30%.[3-5] More recent clinical trials have investigated the efficacy of newer agents including gemcitabine, irinotecan, paclitaxel, capecitabine, and docetaxel (Table 1).[5-14] Notably, gemcitabine and capecitabine are the foci of recent studies, offering a response rate between 24 and 48% and median progression-free survival (PFS) between 4 and 14 months.[8-13] Docetaxel, as a single agent, also produced a response rate of 37% and a median PFS of 5 months.[14]

Doublet Chemotherapy

Platinum doublets are regarded as the principal treatment modality for medically fit patients with metastatic NPC. Clinical trials entailing platinum doublets have exhibited response rates from 20 to

Table 1. Monochemotherapy in recurrent and / or metastatic nasopharyngeal carcinoma with or without pretreatment.

Author(s)	Study	No. of patients	Regimen	OR rate (%)	CR rate (%)	Median PFS	Median OS
Dugan et al[5]	Ph II	108 R + M pretreated	Mitoxantrone	25	NR	4.5 months	13 months
Au et al[6]	Ph II	24 M untreated	Paclitaxel	21.7	0	7.5 months	12 months
Poon et al[7]	Ph II	28 M pretreated	Irinotecan	14	0	3.9 months	11.4 months
Foo et al[8]	Ph II	25 M pretreated	Gemcitabine	28	4	3.6 months	7.2 months
		27 M untreated		48	3.7	5.1 months	10.5 months
Ma et al[9]	Retrospective	18 R + M untreated and pretreated	Gemcitabine	34	6	31% (1 month)	48% (1 year)
Chua et al[10]	Ph II	17 R + M pretreated	Capecitabine	23.5	5.9	4.9 months	7.6 months
Chua et al[11]	Retrospective	49 R + M pretreated	Capecitabine	37	6	5 months	14 months; 54% (1 year)
Ciuleanu et al[12]	Ph II	26 R + M pretreated	Capecitabine	48	9	14 months	62% (1 year)
Zhang et al[13]	Ph II	32 pretreated	Gemcitabine	43.8	0	5.1 months	16 months; 63% (1 year)
Ngeow et al[14]	Ph II	30 R + M pretreated	Docetaxel (weekly)	37	0	5.3 months	12.8 months

Abbreviations: CR = complete response; M = metastatic; NR = not reported; OR = objective response; OS = overall survival; PFS = progression-free survival; Ph II = phase II; R = recurrent.

76%; one study showed that all patients with recurrent disease only responded to cisplatin and 5-FU (Table 2).[9,15-36] Platinum and 5-FU combination therapy is the most popular among doublet regimens widely practised in Asian countries where the disease is endemic. The dose of cisplatin is 100 mg/m^2 on day 1 and that for 5-FU is 1000 mg/m^2 over 3 to 5 days, given every 3 weeks. This popular regimen produced an overall response (OR) rate between 66 and 78% and a median survival of 12 to 14 months.[15-17] In particular, Chi et al[17] revealed that all patients with locally recurrent disease responded to cisplatin, 5-FU and leucovorin producing a median survival of 34 months, while 80% of those with metastatic disease responded with a median survival of 14 months. This regimen was found effective even in patients who had received prior chemotherapy. All five patients who had earlier received mitoxantrone still responded, suggesting a lack of cross-resistance. Another four patients with good responses to prior induction chemotherapy with cisplatin and 5-FU followed by radiotherapy who then developed metastatic disease with disease-free intervals greater than 1 year still, nevertheless, responded to the same regimen.[17] Moreover, the toxicity profile is generally favourable with mild immunosuppression and peripheral neuropathy. However cisplatin-induced nephrotoxicity and ototoxicity were of concern, especially in patients who had also received cisplatin during their previous definitive chemoradiation. Commonly, carboplatin has been used as a substitute of cisplatin for advanced head and neck cancers including NPC.[37] Two older randomised controlled studies on advanced head and neck cancers demonstrated that cisplatin was superior to carboplatin in terms of improved response rate.[38,39] One of these showed cisplatin conferred superior disease-free survival and overall survival (OS) compared to carboplatin when both were used with 5-FU.[39] However this study did not recruit patients with recurrent or metastatic diseases. More recently, carboplatin has been tested with concurrent chemoradiation against cisplatin-based concurrent chemoradiation in a randomised controlled non-inferiority study.[40] Patients with locally advanced NPC were randomised to receive cisplatin chemoradiation versus carboplatin chemoradiation followed by adjuvant chemotherapy using the same platinum compound as in the concurrent phase coupled with 5-FU. No difference in 3-year disease-free survival ($p = 0.9613$) and OS ($p = 0.9814$) was demonstrated.

Table 2. Doublet chemotherapy regimens in recurrent and / or metastatic nasopharyngeal carcinoma with or without pretreatment.

Author(s)	Study	No. of patients	Regimens	OR rate (%)	CR rate (%)	Median PFS	Median OS
Wang and Tan[15]	Retrospective	25 M	Cisp + 5-FU	76	8	NR	NR
Au and Ang[16]	Ph II	24 R + M	Cisp + 5-FU	66	13	8 months	11 months
Chi et al[17]	Ph II	20 R	Cisp + 5-FU / LV	100	15	NR	34 months
		15 M		80	13	NR	14 months
Stein et al[18]	Ph II	18 R + M	Cisp + Ifos	59	15	NR	NR
Yeo et al[19]	Ph II	42 M	Carbo + 5-FU	38	17	NR	12.1 months
Yeo et al[20]	Ph II	27 R + M	Carbo + Pac	59	11	6 months	13.9 months
Tan et al[21]	Ph II	32 M	Carbo + Pac	75	3	7 months	12 months
Ciuleanu et al[22]	Ph II	40 M	Carbo + Pac	27.5	7.5	3.5 months	11.5 months
Ngan et al[23]	Ph II	44 R + M	Cisp + Gem	73	20	10.6 months	15 months
Ma et al[9]	Ph II	14 R + M	Cisp + Gem	64	14	13% (1 year)	68% (1 year)
Wang et al[24]	Retrospective	75 R + M	Cisp + Gem	42.7	5.3	5.6 months	9 months
Ma et al[25]	Ph II	40 R + M	Oxali + Gem	56.1	0	9 months	19.6 months
McCarthy et al[26]	Ph II	9 R + M	Cisp + Doc	22	0	8.4 months	76% (1 year)
Chua et al[27]	Ph II	19 M	Cisp + Doc	62.5	6.3	5.6 months	12.4 months
Li et al[28]	Ph II	48 M	Cisp + Cape	62.5	6.3	7.7 months	13.3 months
Chua et al[29]	Ph II	18 R + M	Ifos + 5-FU / LV	56	6	6.5 months	51% (1 year)
Huang et al[30]	Ph II	34 R + M	Ifos + Doc	67.6	14.7	6 months	NR
Altundag et al[31]	Ph II	21 R + M	Ifos + Doc	33.3	0	7 months	NR
Wang et al[32]	Ph II	39 M	Gem + Vino	36	3	5.6 months	11.9 months
Dede et al[33]	Retrospective	30 R + M	Ifos + Doxo	30	0	4 months (median TTP)	NR
Chen et al[34]	Ph II	61 R + M	Gem + Vino	37.7	1.6	5.2 months	14.1 months
Yau et al[35]	Ph II	15 R + M	Cisp + Pem	20	7	30 weeks (median TTP)	NR
Chua et al[36]	Ph II	44 M	Cisp + Cape	53.8	2.6	7.3 months (median TTP)	28.0 months

Abbreviations: Cape = capecitabine; Carbo = carboplatin; Cisp = cisplatin; CR = complete response; Doc = docetaxel; Doxo = doxorubicin; 5-FU = 5-fluorouracil; Gem = gemcitabine; Ifos = ifosphamide; LV = leucovorin; M = metastatic; NR = not reported; OR = objective response; OS = overall survival; Oxali = oxaliplatin; Pac = paclitaxel; Pem = pemetrexed; PFS = progression-free survival; Ph II = phase II; R = recurrent; TTP = time to progression; Vino = vinorelbine.

In 2013, a retrospective Malaysian study compared cisplatin and 5-FU with carboplatin and 5-FU in 41 patients with recurrent and metastatic squamous-cell head and neck cancer and NPC.[41] This showed that carboplatin and 5-FU (median survival, 12 months) was not inferior to cisplatin and 5-FU (median survival, 10 months; p = 0.110). However, drawbacks of this study were that no subgroup analysis was performed for NPC patients only and there were six treatment-related mortalities (14.6%) — four in the carboplatin + 5-FU group and two in the cisplatin + 5-FU group.

Other active agents for recurrent and metastatic NPC include gemcitabine, capecitabine, oxaliplatin and taxanes.[42] One study published in 2002 tested gemcitabine with platinum as first-line chemotherapy for metastatic NPC in 44 patients and was carried out in Hong Kong.[23] It showed an OR rate of 73% and a median PFS of 11 months. Gemcitabine together with oxaliplatin (a third-generation platinum compound) was also evaluated. This Hong Kong multicentre study found that first-line gemcitabine and oxaliplatin produced an OR of 57% and a median PFS of 9 months.[25] Use of gemcitabine with a non-platinum compound in NPC patients pretreated with platinum was also found to be feasible. A Chinese study including patients all with disease progression while still on previous platinum-based chemotherapy demonstrated an OR rate of 36% and median PFS of 6 months after gemcitabine and vinorelbine.[32] Another Chinese study, in which about 15% of 61 patients had disease progression while still on platinum-based chemotherapy, demonstrated an OR rate of 38%, and a median PFS of 5 months; and the median OS being 14 months following treatment with a median of 4 cycles of gemcitabine and vinorelbine.[34] Use of capecitabine, an oral pro-drug of 5-FU, in combination with cisplatin as first-line treatment was also evaluated. Chua et al[36] published a multicentre study on such treatment in 44 patients with previously untreated metastatic NPC. Of the 39 patients evaluable for efficacy, the OR rate was 54% including one patient (3%) showing a complete response. The median time to progression was 7 months and the median OS was 28 months. In addition, this study specially emphasised quality-of-life assessment using FACT-G and disease-specific FACT-H&N questionnaires.[36] These authors described mild decline in quality-of-life scores after chemotherapy, which was likely due to side-effects and hospitalisation. Docetaxel and ifosphamide doublet chemotherapy regimens were also extensively studied.[27,28,30,31] When used with platinum or non-platinum compounds, OR rates were between 22 and 68% and median PFS ranged between 6 and 8 months.

Most recently a Hong Kong study investigated the role of pemetrexed (a multi-targeted 5-FU analogue) when combined with cisplatin for patients with recurrent or metastatic NPC.[35] When used with regular folic acid and vitamin B12 supplements, pemetrexed per se has very limited treatment-related side-effects. Fifteen patients were recruited into this study, six of whom had locoregional recurrence while the rest had distant metastases with or without locoregional recurrence. Three patients were previously treated with cisplatin-based chemotherapy as prior first-line therapy, while the rest received cisplatin during their initial definitive chemoradiation. Serum biochemistry for Epstein-Barr virus (EBV-DNA) was also monitored as a surrogate tumour marker. The OR rate was 20% and one patient (7%) enjoyed complete remission. Another eight patients (53%) had their disease stabilised, giving an overall clinical benefit rate of 73%; three patients (21%) had undetectable EBV-DNA after treatment. Pemetrexed was well-tolerated; only one patient who had grade 4 anaemia. The most common grade 3 toxicities included neutropenia (27%) and anaemia (20%). No patient developed febrile neutropenia after treatment. As persistent and irreversible treatment-related toxicity often precludes long-term use of chemotherapy, it is hoped that combination regimens with such new agents can offer durable disease control and at the same time minimise toxicities.

It is still under hot debate whether patients can be safely re-challenged with cisplatin if they were exposed to it during previous induction chemotherapy, definitive cisplatin-based chemoradiation or prior palliative chemotherapy. An older study revealed that all four patients with a disease-free interval of more than 1 year after induction cisplatin and 5-FU and radiotherapy still responded to the same regimen.[17] In their study on doublet regimen using cisplatin and capecitabine for previously untreated metastatic NPC, Chua et al[36] demonstrated that prior adjunctive (neoadjuvant, concurrent, or adjuvant) chemotherapy given at least 6 months before study entry had a longer PFS (9 vs. 7 months) and OS (30 vs. 28 months), though the differences were not statistically significant. Recently, molecular medicine has played an important role in the prediction of chemosensitivity. Some light has been shed on the discovery of excision repair cross complementation group 1 (ERCC1) and xeroderma

pigmentosum complementation group F (XPF) involved in the repair cisplatin-DNA adducts via different pathways. These have a bearing on the nucleotide excision repair pathway, double-strand break repair, and repair of interstrand crosslinks.[43-48] When associated with ERCC1, XPF forms a heterodimer which functions as a structure-specific endonuclease. The ERCC1 also binds and stabilises XPF, which enhances the latter's endonuclease to create an incision 5' to the DNA lesion, thus allowing DNA to be repaired. Four studies confirmed that high expression levels of ERCC1 conferred poor treatment outcomes in NPC when cisplatin was administered as induction treatment, concurrently with radiation therapy or palliative setting.[43-46] Another study showed that high ERCC1 levels predicted poor locoregional control, but did not predict resistance to cisplatin.[47] One more recent study showed that neither ERCC1 nor XPF predicted locoregional recurrence, disease-free survival and OS in 142 patients with NPC treated with curative intent.[48] Perhaps one of the solutions to these conflicting results is to re-biopsy the recurrent / metastatic lesions to evaluate chemosensitivity to platinum.

Overall, all these published trials should be interpreted with great caution, due to small sample sizes, the nature of phase II studies, patient population heterogeneity (locoregional recurrence alone vs. distant metastasis), and variations in prior lines of systemic chemotherapy (especially if platinum-based). Notwithstanding the limitations of these clinical and molecular studies, we recommend cisplatin, preferably with 5-FU, as the first choice due to the long history and experience with these agents, especially for chemo-naïve patients. When length of hospital stay becomes an issue, 5-FU may be substituted by newer agents such as capecitabine, gemcitabine, and taxanes. For second-line or subsequent treatment of metastasis, whether platinum-based chemotherapy was given previously is a consideration. For patients treated with platinum-based chemotherapy, subsequent treatment depends on performance status, toxicity, and the interval to recurrence after previous platinum-based regimen. Re-challenge with cisplatin and 5-FU can be considered in patients who enjoyed a good initial response to the same regimen with an intervening disease-free period of more than 1 year. Carboplatin is an acceptable substitute producing similar responses and outcomes when cisplatin is contraindicated, though it generally gives rise to more haematological toxicities. For patients who fail platinum and 5-FU or whose disease relapse within a year of such a regimen, second-line treatment including gemcitabine, capecitabine, or taxanes with or without platinum can be considered.

Polychemotherapy

Use of more than doublet combination chemotherapy has not been shown to be superior to doublet counterparts. Several trials reported on the polychemotherapy for recurrent NPC and demonstrated encouraging response rates but also more treatment-related toxicities (Table 3).[49-56] More importantly, they have not been compared with the standard 5-FU + cisplatin doublet regimen. One study, CAPABLE, incorporating five compound (cisplatin, methotrexate, bleomycin, cyclophosphamide, and doxorubicin), was associated with a response rate of 80% but also an extraordinarily high treatment-related mortality of 12%.[52] Another phase II study, using 5-FU, mitomycin, epirubicin, and cisplatin demonstrated a response rate of 52% at the expense of iatrogenic death of 9%.[54] In general, polychemotherapy entailing three or more agents is not routinely recommended.

Table 3. Results for polychemotherapy in recurrent and / or metastatic nasopharyngeal carcinoma with or without pretreatment.

Author(s)	Study	No. of patients	Regimens	OR (%)	CR (%)	Median PFS	Median OS
Boussen et al[49]	Ph II	49 R + M untreated and pretreated	Cisp + B + 5-FU	79	19	50 months	NR
Su et al[50]	Ph II	25 R + M	Cisp + B + 5-FU	40	3	NR	NR
Azli et al[51]	Ph II	44 R + M pretreated and not	BEC (B + Epi + Cisp)	45	20	53 months	NR
Siu et al[52]	Ph I / II	17 R	CAPABLE	41	23.5	NR	16 months
		44 M		80	6.8	NR	14 months
Taamma et al[53]	Ph II	23 R + M	FBEC (5-FU + B + Epi + Cisp)	78	39	42 months	NR
Hasbini et al[54]	Ph II	44 R + M	FMEP (5-FU + mitomycin + Epi + Cisp)	52	13	9 months	14 months
Leong et al[55]	Ph II	28 M	Carbo + Gem + Pac + 5-FU / LV	86	11	8 months	22 months
Huang et al[56]	Ph II	56 R + M	DCF (Doc + Cisp + 5-FU)	72.5	9.8	NR	NR

Abbreviations: B = bleomycin; CAPABLE: Cyclophospamide + Bleomycin + Doxorubicin + Cisplatin; Carbo = carboplatin; Cisp = cisplatin; CR = complete response; Doc = docetaxel; Epi = epirubicin; 5-FU = 5-fluorouracil; Gem = gemcitabine; Ifos = ifosphamide; LV = leucovorin; M = metastatic; NR = not reported; OR = objective response; OS = overall survival; Pac = paclitaxel; PFS = progression-free survival; Ph II = phase II; R = recurrent.

PALLIATIVE TARGETED THERAPY

A number of studies have tested the efficacy of targeted therapy for metastatic NPC. First of all, like other squamous-cell head and neck cancers, epidermal growth factor receptor (EGFR) is also highly expressed in NPC.[57-59] Thus, a few studies investigated the role of EGFR tyrosine kinase inhibitors and monoclonal antibodies in metastatic NPC. A small phase II study from Hong Kong showed that none of 19 patients responded after gefitinib in previously heavily pretreated NPC, with median values for time to progression and OS of 4 and 16 months, respectively.[60] Another Hong Kong study was terminated due to lack of efficacy following treatment with gefitinib.[61] Likewise, a phase II study, using erlotinib as maintenance treatment after 6 cycles of gemcitabine and cisplatin in chemo-naïve patients with metastatic NPC, revealed stable disease in only three out of 12 evaluable patients.[62] Thus, erlotinib appeared to be no better than geftinib in metastatic NPC. Use of cetuximab, a monoclonal antibody against EGFR, in combination with carboplatin was also tested. Seven (12%) out of 59 patients enjoyed a partial response with a median PFS of 3 months and median OS of 8 months, but at the expense of significant toxicity (grade ≥3 toxicities in 52% of the patients).[63]

Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) is also a potential target of treatment in NPC. Its overexpression was found in 60 to 67% of patients and also conferred a shorter survival.[64,65] The use of sorafenib, an oral multikinase inhibitor, was also not shown to be more efficacious than systemic chemotherapy.[66] A more recently published phase II study on sorafenib in combination with standard cisplatin and 5-FU regimen in the induction phase followed by maintenance sorafenib until disease progression demonstrated a high response rate of 78% and median PFS of 7 months and median OS of 12 months.[67] However, this regimen was also accompanied by a high frequency of hand-foot-skin reactions (83% in all and 19% in grade ≥3), leucopenia (78% in all and 7% in grade ≥3), and haemorrhagic events (22% in all and 2% in grade ≥3). Another multikinase tyrosine kinase inhibitor sunitinib was also tested in metastatic NPC in Hong Kong.[68] Of the 10 patients who had post-treatment radiological assessment for tumour response, one patient had a partial response and another three remained stable for at least 12 months. Meanwhile, the haemorrhagic events also deserve attention (64% in all, 29% in grade 3/4, and 14% in grade 5) and included epistaxis, haemoptysis, and haematemesis in 6, 3, and 2 patients, respectively. Two patients with tumour invasion to the carotid sheath suffered a fatal epistaxis / haematemesis which was likely secondary to carotid blowout after tumour shrinkage. Pazopanib, another orally available multikinase inhibitor against VEGFR-1, -2, and -3, platelet-derived growth factor (PDGF)-α, PDGF-β and c-kit tyrosine kinases was also evaluated in NPC.[69] Two (6%) out of 33 patients enjoyed a partial response and another 16 (48%) patients had stable disease. Treatment was fairly tolerated; fatigue and hand-foot syndrome were the commonest grade ≥3 toxicities. One patient died of epistaxis and myocardial infarction. At around the same time, bevacizumab, an anti-angiogenic monoclonal antibody, was also shown to produce promising responses when combined with cisplatin chemoradiation as the definite treatment for locally advanced NPC.[70] Whether the effect of bevacizumab and systemic chemotherapy can also accrue in a metastatic setting will depend on results from future studies.

New genes and / or growth factor pathways have been identified as potential targets of new targeted therapies. For instance, the PI3K/Akt pathway was recently revealed to be frequently involved in NPC tumourigenesis and progression.[71,72] Apart from that, microRNAs (miRNAs), a diverse class of 20-24–nucleotide non-coding RNAs were also found upregulated in NPC compared with non-tumorous nasopharyngeal tissues.[73-78] A local study found that upregulation of miRNA-144 promoted malignant progression by repressing the expression of a tumour suppressor gene phosphatase and tensin homologue (PTEN), which is partially responsible for upregulation of the PI3K/Akt pathway in NPC.[65] In-vitro cell-line studies have demonstrated that Akt inhibitors can suppress tumour growth. Hopefully the efficacy of these inhibitors can be further verified in phase II and III clinical trials.[79,80]

CONCLUSION

In summary, a platinum-based chemotherapy regimen especially cisplatin and 5-FU is still the principal first-line treatment for recurrent / metastatic NPC. Cisplatin is preferred over carboplatin based on its long history with much accumulated experience by oncologists. However, other factors including the toxicity profile of chemotherapy, renal function, and length of stay in hospital for protracted 5-FU infusions should be taken into account when considering this regimen. Newer chemotherapeutic agents like gemcitabine, capecitabine

and taxanes can be safely combined with platinum compounds either as first-line or subsequent-line therapy to substitute for 5-FU, especially when hospitalisation is a major concern. Combination chemotherapy using three or more agents has not been shown superior to doublet regimens. The role of targeted therapy in NPC is still evolving. New targets and growth factor pathways have been gradually identified and new compounds against these targets are awaited. Current attention is also focused on immunotherapy, using autologous EBV-specific cytotoxic T-lymphocytes (CTLs) targeting the antigens of EBV including EBNA-1, latent membrane protein-1 (LMP-1) and latent membrane protein-2 (LMP-2).[81,82] Previous pilot studies have demonstrated that CTL immunotherapy is well tolerated without any immunosuppressive effects on bone marrow as seen in chemotherapy.[83-87] One pilot study conducted by Secondino et al[86] showed an OR rate of 27% and disease control rate of 55% in a series of 11 patients. Preliminary results of using a novel adenoviral vector-based vaccine (AdE1-LMPoly) that encodes multiple CTL epitones from LMP1 and LMP2 are also promising.[87] With all these novel ideas and treatment options, we anticipate a new paradigm of systemic treatment for metastatic NPC in the near future.

DECLARATION

No conflicts of interest were declared by the authors.

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