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Nasopharyngeal Carcinoma: The Role for Chemotherapeutics and Targeted Agents

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1. Introduction

Nasopharyngeal carcinoma (NPC) is a distinguishing and rare form of head and neck cancer whose predominant tumor type arises in the nasopharynx, the narrow tubular passage behind the nasal cavity. The disease is classified into three histopatholigical types by The World Health Organization (WHO): Keratinizing squamous cell carcinoma (SCC, WHO Type I), Nonkeratinizing carcinoma: differentiated (WHO Type II) and undifferentiated (WHO Type III) and basaloid squamous cell carcinoma[1]. Worldwide, there are 80,000 incident cases and 50,000 deaths annually,[2] however the disease is vastly more common in certain regions in Asia and Africa than anywhere else in the world. In the United States, the incidence ranges from 0.2 and 0.5 cases per 100,000 population, which constitutes roughly 0.02% of all cancers, compared with endemic areas such as areas in Asia, where NPC might represent 25% of all cancers[3]. In fact, it is sometimes referred to as Cantonese cancer because it occurs in about 25 cases per 100,000 people in this region, 25 times higher than the rest of the world[4].

Making it distinct is the fact that it differs from other head and neck squamous cell carcinomas (HNSCCs) in epidemiology, histology, natural history, and response to treatment. The remarkable geographic and demographic variation of NPC incidence suggests a multifactorial etiology of NPC. In endemic populations, the risk of NPC appears to be related to an interaction of these factors, namely Epstein-Barr virus (EBV) infection; genetic predisposition; and environmental factors such as the traditionally high intake of preserved foods[5-7].

2. RT and chemotherapy for locally advanced disease

The radiosensitizing properties of systemic chemotherapy are firmly established for head and neck tumors[8], and NPC is inherently more chemosensitive than other head and neck malignancies[9]. Therefore, it follows intuitively that adding systemic chemotherapy or targeted therapies to radiotherapy could provide NPC patients with additional clinical benefit. This hypothesis was tested in the late 1990s, and the utility of platinum-based chemotherapy in addition to radiation (RT) in locally advanced NPC was clearly

demonstrated in 1998 when the Intergroup 0099 trial was terminated prematurely due to a clear survival benefit in the chemotherapy with radiotherapy arm[10]. Since that time several randomized trials have been published, all varying in their chemotherapy regimens and timing of chemotherapy in relation to RT (Tables 1 and 2).

Trial	No. of pts	Treatment Arms
Neoadjuvant + RT vs RT alone		
VUMCA (1996)	a: 171	a: Bleomycin/Epirubicin/Cisplatin → RT
	b: 168	b: RT
Chua et al (1998)	a: 167	a: Cisplatin/Epirubicin → RT
	b: 167	b: RT
Ma et al (2001)	a: 224	a: Cisplatin/Bleomycin/5-FU → RT
	b: 225	b: RT
Hareyama et al (2002)	a: 40	a: Cisplatin/5-FU → RT
	b: 40	b: RT
Concurrent + RT vs RT alone		
Lin et al (2003)	a: 141	a: Cisplatin/5-FU + RT
	b: 143	b: RT
Chan et al (2002, 2004)	a: 174	a: Cisplatin + RT
	b: 176	b: RT
Zhang et al (2005)	a: 59	a: Oxaliplatin + RT
	b: 56	b: RT
Adjuvant + RT vs RT alone		
Rossi et al (1988)	a: 113	a: RT → Vincristine/Cyclophosphamide/Adriamycin
	b: 116	b: RT
Chi et al (2002)	a: 77	a: RT → Cisplatin/Fluorouracil/Leucovorin
		b: RT
Neoadjuvant + Adjuvant + RT vs RT alone		
Chan et al (1995)	a: 37	a: Cisplatin/Fluorouracil → RT → Cisplatin/5-FU
	b: 40	b: RT
Concurrent + Adjuvant + RT vs RT alone		
Al-Sarraf et al (1998, 2001)	a: 93	a: Cisplatin + RT → Cisplatin/5-FU
	b: 92	b: RT
Wee et al (2005)	a: 111	a: Cisplatin + RT → Cisplatin/5-FU
	b: 110	b: RT
Lee et al (2005, 2010)	a: 172	a: Cisplatin + RT → Cisplatin/5-FU
	b: 176	b: RT
Lee et al (2006)	a: 51	a: Cisplatin + RT → Cisplatin/5-FU
	b: 44	b: Cisplatin + AF RT → Cisplatin/5-FU
	c: 52	c: AF RT
	d: 42	d: RT
Kwong et al (2004)	a1: 57	a1: Uracil-Tegafur + RT → Cisplatin/5-FU,Vincristine/Bleomycin/MTX
	a2: 53	a2: Uracil-Tegafur + RT
	a3: 54	a3: RT → Cisplatin/5-FU, Vincristine/Bleomycin/MTX
	b: 55	b: RT
Chen et al (2008)	a: 158	a: Cisplatin + RT → Cisplatin/5-FU
	b: 158	b: RT

Table 1. Randomized Trials of Chemotherapy with RT vs RT alone in locally advanced NPC

Trial	Treatment Arm	OS	DFS	Median F/U (mo)
Neoadjuvant + RT vs RT alone				
VUMCA (1996)	a	3yr – 60%	3yr – 52%*	49
	b	54%	32%	
Chua et al (1998)	a	3yr – 78%	3yr – 48%	30
	b	71%	42%	
Ma et al (2001)	a	5yr – 63%	5yr – 59%*	62
	b	56%	49%	
Hareyama et al (2002)	a	5yr – 60%	5yr – 55%	49
	b	48%	43%	
Chua (2005)	a	5yr – 62%	5yr – 51%*	67
	b	58%	43%	
Concurrent + RT vs RT alone				
Lin et al (2003)	a	5yr – 72%*	5yr – 72%*	65
	b	54%	53%	
Chan et al (2002, 2004)	a	NR	2yr – 76%	33
	b	NR	69%	
	a	5yr – 70%	5yr – 60%	65
	b	59%	52%	
Zhang et al (2005)	a	2yr – 100%*	2yr – 96%*	24
	b	77%	83%	
Adjuvant + RT vs RT alone				
Rossi et al (1998)	a	5yr – 55%	5yr – 54%	49.5
	b	61%	50%	
Chi et al (2002)	a	4yr – 59%	4yr – 58%	43
	b	67%	56%	
Neoadjuvant + Adjuvant + RT vs RT alone				
Chan et al (1995)	a	2yr – 80%	2yr – 68%	28.5
	b	81%	72%	
Concurrent + Adjuvant + RT vs RT alone				
Al-Sarraf et al (1998, 2001)	a	3yr – 76%*	3yr – 66%*	32.4
	b	46%	26%	
	a	5yr – 67%*	5yr – 58%*	60
	b	37%	29%	
Wee et al (2005)	a	2yr – 85%*	3yr – 80%*	38.4
	b	78%	65%	
Lee et al (2005, 2010)	a	3yr – 77%	3yr – 69%	25
	b	76%	61%	
	a	5yr – 68%	5yr – 62%*	70.8
	b	64%	53%	
	a	8yr – 61%	NR	
	b	54%	NR	
Lee et al (2006)	a	3yr – 87%	3yr – 73%	33
	b	88%	88%	
	c	73%	63%	
	d	83%	65%	
Kwong et al (2004)	a1	3yr – 89%	3yr – 70%	32.5
	a2	84%	69%	
	a3	71%	54%	
	b	83%	61%	
Chen et al (2008)	a	2yr – 90%*	2yr – 85%*	29
	b	80%	73%	

* statistically significant result

Table 2. OS and DFS of randomized trials of chemotherapy with RT vs. RT alone in locally advanced NPC

2.1 Neoadjuvant chemotherapy

Four trials have assessed the role of neoadjuvant chemotherapy followed by RT versus RT alone. The VUMCA study[11], active from 1989-1993, was a multi-center phase II trial of 339 patients, in which 171 patients were randomized to receive neoadjuvant bleomycin, epirubicin, and cisplatin (BEC). The remaining 168 patients received RT alone. After a median followup of 49 months the authors noted increased disease free survival (DFS) in the chemotherapy with RT arm (52% vs 32%). However, no difference in overall survival (OS) was seen, and the trial was notable for an 8% rate of treatment-related death in the experimental arm versus 1% among patients treated with RT alone.

A small study of 80 patients, active from 1991-1998, was published by Hareyama et al[12]. Forty patients were randomized to cisplatin and 5-fluorouracil prior to RT, and the control arm received RT alone. A trend toward both OS and DFS at three years was seen in the neoadjuvant arm (60% and 55% vs 48% and 43%, respectively), though this did not reach statistical significance. In 1998, Chua et al published the results of a trial active from 1989-1993, in which 334 patients were randomized to either cisplatin and epirubicin with RT or RT alone[13]. Intention to treat analysis at three years revealed a trend toward improved DFS and OS in the chemoradiotherapy arm (58% and 80% vs 46% and 72%, respectively), however the results did not reach statistical significance.

In 2001 Ma et al reported a trial, active from 1993-1994, in which 449 patients were randomized to two to three cycles of cisplatin, 5-fluorouracil, and bleomycin with RT versus RT alone[14]. Intention to treat analysis at five years revealed a statistically significant improvement in DFS (59% vs 49%), however, while a trend toward improved OS was noted this did not reach statistical significance. In 2005, Chua published an analysis of pooled data from the latter two trials, which together included 784 patients with a median follow up of 67 months[15]. This analysis revealed a statistically significant DFS benefit in the neoadjuvant arm (51% vs 43%). However, consistent with the other trials, a trend toward OS (62% vs 58%) did not reach statistical significance. In summary, four trials of neoadjuvant platinum-based chemotherapy in addition to RT have revealed, at best, modest improvement in DFS and a trend toward improved overall survival. However to date no trial has shown a clear and statistically significant survival benefit with the neoadjuvant strategy.

2.2 Concurrent chemotherapy

To date, three trials have assessed the strategy of concurrent chemotherapy and RT as compared to RT alone. In 2002, Chan et al reported a trial, active from 1994-1997, of 350 patients randomized to weekly low-dose cisplatin plus RT versus RT alone[16]. Notably, the study population in this trial had relatively advanced disease: 90% of patients were Ho's stage III or IV, and over 70% were AJCC stage III or IV. A trend toward improved DFS at two years was seen (76% vs 69%), however this did not reach statistical significance. Updated data published in 2005 revealed modestly improved DFS and OS for the chemotherapy arm at five years: DFS was 60% and 52% ($p = 0.06$) and OS was 70% and 59% ($p = 0.05$) for the chemotherapy + RT and RT alone arms, respectively[17]. A subgroup analysis of this data revealed that patients with more advanced disease (T3 and T4) derived the most benefit. Lin et al reported data in 2003 from a 1993-1999 study of concurrent cisplatin and 5-fluorouracil plus

RT vs RT alone[18]. All patients in this trial had AJCC stage III or IV disease. The study revealed statistically significant improvement in both DFS and OS with concurrent chemotherapy: 5-year OS rates for the chemotherapy arm were 72% compared with 54% in the control arm, and the 5-year DFS rates were 72 versus 53%, respectively. Of note, significantly more toxicity was noted in the chemotherapy arm. In 2005, Zhang et al published a trial, active from 2001-2003, of 115 patients randomized to six doses of weekly oxaliplatin plus concurrent RT versus RT alone[19]. Consistent with the earlier cisplatin-based trials, this study revealed a significant DFS and OS benefit for patients treated with concurrent platinum-based chemotherapy. For the chemotherapy + RT and RT alone arms, respectively, two year OS was 100% versus 77% and two year DFS was 96% versus 83%. In summary, three trials of concurrent platinum-based chemotherapy plus radiotherapy have revealed statistically significant improvements in DFS and OS as compared to radiotherapy alone. In these trials, the benefit was greatest in patients with advanced disease.

2.3 Adjuvant chemotherapy

The first trial that addressed the question of adding chemotherapy to RT for patients with NPC used an adjuvant strategy. In 1988, Rossi et al published the results of a 4 year multi-center trial, active from 1979-1983, in which 229 patients were randomized to either adjuvant vincristine, cyclophosphamide, and adriamycin following RT or RT alone[20]. Follow up at four years did not reveal a statistically significant difference in DFS or OS between the two groups. Notably, no platinum agent was used in this trial, and therefore the lack of benefit must be interpreted in light of subsequent studies which have established platinum-based chemotherapy as the cornerstone of chemotherapy plus RT strategies in this disease. However, a later study of adjuvant chemotherapy, which did include cisplatin, was published in 2002 by Chi et al and revealed no significant DFS or OS benefit[21]. Between 1994 and 1999, 157 patients were randomized to either adjuvant cisplatin with 5-fluorouriacil and leucovorin plus RT versuss RT alone. At five years, the DFS rates were 54.4% vs 49.5% and the OS rates were 60.5% and 54.5%, respectively, for the chemotherapy and RT arms. Neither of these differences reached statistical significance. In summary, two trials have addressed the strategy of adjuvant chemotherapy following RT, one of which was published prior to the Intergroup 0099 trial and as such did not include a platinum agent. Neither study revealed a statistically significant improvement in survival with adjuvant chemotherapy following RT as compared to RT alone.

2.4 Neoadjuvant plus adjuvant chemotherapy

To date, only one study has assessed the effect of combined neoadjuvant and adjuvant chemotherapy in addition to RT. In 1995, Chan et al reported a study of 82 patients randomized to two cycles of neoadjuvant and four cycles of adjuvant chemotherapy (both with cisplatin) plus RT vs RT alone[22]. No difference in either DFS or OS was noted after two years follow up. In summary, the single published trial of combined neoadjuvant and adjuvant chemotherapy (cisplatin) plus RT revealed no benefit of this strategy as compared to RT alone.

2.5 Concurrent plus adjuvant chemotherapy

To date, the most influential study to address the question of chemotherapy plus RT in locally advanced NPC utilized a combined concurrent and adjuvant platiunum-based

chemotherapy strategy, and, consequently, this approach has subsequently received the most research attention. In 1998, Al-Sarraf et al published the results of the Intergroup 0099 study, active between 1989 and 1995, in which 193 patients were randomized to either RT alone or a chemotherapy arm[10]. Patients in the chemotherapy group were treated with cisplatin on days 1, 22 and 43 of the concurrent RT, and three adjuvant cycles of cisplatin with 5-fluorouracil were given monthly after completion of chemoradiotherapy. At 3 years, DFS was 69% in the chemotherapy group and 24% in the RT alone arm. Overall survival at 3 years was 78 *vs* 47%, favoring chemotherapy. These results prompted early closure of the study, given the clear benefit demonstrated with concurrent plus adjuvant cisplatin. Updated analysis at 5 years confirmed the benefit of treatment, with 5-year DFS rates of 58 *vs* 29% and 5-year OS rates of 67 *vs* 37%, both favoring the combined therapy arm[23]. Analysis of the National Cancer database since the first published results of the Intergroup 0099 study data in 1998 has demonstrated that this study has led to a demonstrable change in NPC management. Of all patients enrolled in the database and matching the eligibility criteria of the Intergroup 0099 study, only 38% received chemotherapy along with RT prior to 1997, while since the publication of the data, 65% of these patients have received concurrent and adjuvant chemotherapy[24].

One-quarter of all patients treated on the Intergroup 0099 protocol had World Health Organization (WHO) stage I histology (keratinizing squamous cell carcinoma). A phase III randomized trial active from 1997-2003, using a similar chemotherapy and RT plan but restricted to patients with WHO type IIa (nonkeratinising squamous cell carcinoma) and IIb (undifferentiated carcinoma) histologies was published by Wee et al in 2005[25]. The two and three year DFS and OS rates were statistically significant and favored the use of chemotherapy, confirming the findings of the Intergroup 0099 trial. Of note, the chemotherapy regimen used in the Wee et al study differed slightly from the Intergroup 0099 trial in that the dose of cisplatin was given in divided doses rather than one dose, however, the total dose remained the same. Lee et al have published data from the Hong Kong NPC Study Group in which the Intergroup 0099 regimen was applied to patients with nonkeratinizing or undifferentiated NPC[26]. Preliminary results published in 2004 suggested a trend toward improved DFS in the chemotherapy arm. Long term follow up data published in 2010 confirmed the trend toward improved DFS seen on the initial analysis (62% vs 53% favoring chemotherapy). However, while five-year analysis showed a clear reduction death due to disease progression in the chemotherapy arm (28% vs 38% favoring chemotherapy, $p = 0.08$), the five-year overall survival data revealed only a modest trend favoring chemotherapy (68% vs 64%, $p = 0.22$)[27]. The discrepancy between a clear decreased in disease-associated death and nearly identical five-year overall survival was attributed to an increase in non-cancer deaths among patients in the chemotherapy arm.

A similar trial, also published by Lee et al, utilized the identical chemotherapy as IG-0099, but assessed both the therapeutic gain with concurrent and adjuvant chemotherapy and/or accelerated RT[28]. Four arms were evaluated, conventional RT vs. accelerated fraction RT vs. conventional RT with concurrent and adjuvant chemotherapy vs. accelerated fraction RT with concurrent and adjuvant chemotherapy. After 189 patients were randomized, the study was closed due to poor accrual. Preliminary data after a median follow-up of 2.9 years, showed no statistically significant change in either OS or DFS at 3-years.

In 2008, Chen et al published the results of a study of 316 patients performed between 2002 and 2005, in which subjects randomized to the chemotherapy arm received weekly cisplatin concurrent with RT, followed by cisplatin and 5-fluorouracil every four weeks for three cycles following completion of RT[29]. Preliminary analysis after two years revealed a statistically significant difference in both overall (89.8% vs 79.7%) and disease free (84.6% vs 72.5%) survival, favoring chemotherapy, at the expense of increased toxicity in the chemotherapy arm.

Finally, a factorial study of four different regimens was published by Kwong et al in 2004[30]. This study assessed the combination of RT alone *vs* three other schemas: RT with adjuvant chemotherapy, concurrent chemoradiotherapy and lastly, concurrent chemoradiotherapy followed by adjuvant chemotherapy. UFT (uracil an tegafur in a 4:1 molar ratio) was given concurrent with RT, while the adjuvant therapy consisted of alternating cycles of cisplatin/5-fluorouracil and vincristine/bleomycin/methotrexate.

Although a trend towards improved DFS and OS was noted with the addition of concurrent chemotherapy, it did not reach statistical significance at 3 years. In assessing distant metastases rates, a significant reduction was attributable to concurrent chemotherapy. In this study, adjuvant chemotherapy did not improve outcome.

3. Chemotherapy for recurrent and metastatic disease

The management of recurrent and metastatic NPC remains challenging. Several studies have evaluated the use of platinum drugs in combination with various other chemotherapeutic agents including gemcitabine [31,32], bleomycin-5FU[33], 5FU[34], capecitabine[35], bleomycin/epirubicin/5FU[36], paclitaxel[37], and docetaxel[38]. Given the known chemosensitivity of NPC, it is not surprising that these regimens are associated with good overall response rates, ranging from 56% - 79%. However, the duration of response is short, and median overall survival in these trials was on average approximately one year (range: 11 – 25 mo). Two trials of non-platinum based monotherapy (gemcitabine[39] and capecitabine[40]) were associated with worse overall response rates (28% and 37%, respectively) and similar median overall survival (7.2 and 14 months, respectively). Adding vinorelbine to gemcitabine for patients with platinum-resistant disease yielded an overall response rate of 36% with a median overall survival of 11.9 months[41]. Irinotecan used as monotherapy in heavily pretreated patients has been associated with an overall response rate of 14% (all partial responses) and median overall survival of 11.4 months[42]. The poor clinical outcomes associated with traditional chemotherapeutic agents underscores the urgent need for new and more effective therapeutic options in the locally advanced and metastatic setting.

4. Targeted therapy

Given the poor clinical outcomes associated with chemotherapeutics in the metastatic setting, evaluation of targeted therapies become of utmost importance (Table 3).

Epidermal growth factor receptor (EGFR) expression in NPC has been correlated with decreased survival, increased rates of locoregional failure, and more aggressive disease [43,44]. Drawing on those findings, Chan et al published a study in 2005 evaluating the anti-EGFR

Table 3. Targeted therapy in NPC

Reference	Targeted Tx	Other Tx	# of patients/ # evaluable	Disease Status	Overall Respons
Chan (2005)	Cetuximab	Carboplatin	60/59	Recurrent/Metastatic	11.7% (1
Ma (2007)^	Cetuximab	Cisplatin + IMRT	20/12	Locally advanced	83%
Elser (2007) (3)	Sorafenib	None	7/NR	NR	N/A (4)
Chua (2008)	Gefitinib	None	19/NR	Recurrent/Metastatic	0%
Ma (2008)	Gefitinib	None	16/15	Recurrent/Metastatic	0%
You (2009)^	Erlotinib	Cisplatin/Carboplatin + Gemcitabine (5)	20/11	Recurrent/Metastatic	0%

(1)All partial responses
(2)No composite grade 3/4 toxicity data reported. Reports that 85% of patients experienced grade 3/4 leuk
grade 3/4 mucositis.
(3)This study included both SCCHN and NPC patients. Data is presented here only for the 7 NPC patients
(4)One of 26 evaluable SCCHN/NPC patients had a partial response. However, it is not reported whether
(5)Erlotinib was given as maintenance after completion of 6 cycles platinum + gemcitabine or as 2nd line th
chemotherapy
(6)Reports grade 3/4 toxicity as "rare", most common was rash in (33%)
^ Abstract

monoclonal antibody, cetuximab, in combination with carboplatin[45]. This multi-center phase II trial enrolled 60 patients, all of who had evidence of disease progression within 12 months of platinum-based chemotherapy. Notably, 93.3% of patients in this trial had stage IV disease at the time of enrollment, and 85% had distant metastases. The treatment protocol consisted of carboplatin infused every three weeks for a maximum of eight cycles, along with cetuximab 400mg/m2 followed by 250mg/m2 weekly. The median number of cetuximab infusions completed was 10, with a range of 1-30. Only 53.3% of the patients received at least 3 carboplatin infusions. Of patients enrolled, 11.7% had a partial response to therapy; no complete responses were observed in this study and 48.3% of patients had stable disease. Median time to progression was 81 days, and median overall survival was 233 days. Grade 3 or 4 toxicity was observed in 51.7% of patients, 31.7% of whom had toxicity that was attributed to cetuximab. A subsequent trial of cetuximab in combination with cisplatin-IMRT was reported in abstract form by Ma et al in 2008[46]. The 20 patients in this trial differed from those in Chan et al in that all subjects had untreated, non-metastatic disease. The cetuximab dosing was the same (400mg/m2 initially, followed by 250mg/m2 weekly). Cisplatin was administered at 30mg/m2 weekly, along with weekly IMRT. Ninety percent of patients received at least 5 doses of cetuximab, and 80% received at least 5 cisplatin infusions. Preliminary analysis at 3 months revealed promising results: of 12 patients evaluable for response, 10 had a complete response and the remaining two had stable disease.

Two studies have evaluated the use of the small molecule EGFR tyrosine kinase inhibitor, gefitinib, as monotherapy in advanced platinum-resistant NPC. In 2008 Chua et al reported a single-center phase II study of 19 patients with relapsed or progressive despite at least two prior chemotherapy regimens (one of which included a platinum drug)[47]. In contrast to the previously mentioned trials, this study protocol assessed response to anti-EGFR therapy alone without any concurrent chemotherapeutic agent. Patients in the study received gefitinib 250mg daily until disease progression, unacceptable toxcitiy, or patient refusal. Median treatment duration was 10 weeks; 63% of patients were taken off study due to disease progression, and the remaining patients expressed a preference not to continue treatment. The regimen was well tolerated, with no grade 3 or 4 toxicity reported. Unfortunately, no patients in this study achieved either partial or complete response. Similar disappointing results were reported by Ma et al in 2008[48]. In that trial, 16 patients with progressive disease after prior platinum-based therapy were treated with oral gefitinib 500 mg/day. Three patients achieved stable disease (range: 2.8 – 8.5 months), and the drug was generally well tolerated. However, consistent with the results reported by Chua et al, no patient achieved a partial or complete response. In 2009, You et al presented data in abstract form reporting their study of the EGFR tyrosine kinase inhibitor, erlotinib[49]. In that small trial of 20 patients, subjects were first treated with up to 6 cycles of gemcitabine + a platinum agent (either cisplatin or carboplatin), followed by erlotinib 150 mg/day as maintenance (if stable disease) or 2nd line therapy (if progressive disease prior to 6 chemotherapy cycles). Of the 11 patients evaluable for response to erlotinib, three had stable disease that was maintained for 3, 4, and 7 months.

Sorafenib, a multi-kinase inhibitor with activity against VEGFR-2, VEGFR-3, PDGFR, FLT-3, c-kit, and the Raf isoforms c-Raf and b-Raf, was evaluated in a 2007 study published by Elser et al.[50] Of particular theoretical interest is the anti-angiogenesis activity of sorafenib

mediated by its activity against the vascular endothelium growth factor receptor (VEGFR), given the known VEGF overexpression in NPC[51-53]. Notably, this study was not limited to NPC and also enrolled patients with SCCHN; of 27 patients enrolled, only 7 had NPC. Patients received sorafenib 400 mg twice daily as monotherapy, and therapy was generally well tolerated with few grade 3 or 4 toxicities. Although the reported response data for the entire patient cohort was promising (9 of 26 evaluable patients had stable disease, and one had a partial response), response data specific to the NPC subgroup was not separately reported. Median time to progression for the 7 patients with NPC was 3.2 months, and median overall survival was 7.7 months.

In addition to monoclonal antibody and small molecule targeted therapy, immunotherapy may play a role in the future management of NPC. This approach has great theoretical appeal in NPC, given the strong association with Epstein-Barr virus (EBV). NPC cells express two distinct EBV latent membrane proteins, LMP-1 and LMP-2, and these proteins represent targets for adoptive immunotherapy[54]. In a phase I study published by Straathof et al in 2005, 10 patients with advanced NPC were treated with EBV-specific cytotoxic T lymphocytes (CTL)[55]. Four patients were in remission at the time of enrollment, and all remained disease-free 19–27 months after infusion. Of the remaining 6 patients, all with relapsed or refractory disease, 2 had complete responses, 1 had a partial response, 1 had stable disease and 2 had no response. CTL was well tolerated in this study. Follow up data from the same group was published in 2010, and this again demonstrated clinical benefit following CTL infusion[56]. Of 23 patients in this study (all with a history of relapsed/refractory NPC), 8 were in remission and 15 were not. Of the 8 patients in remission, 5 remained disease free at the time of publication (range: 17-75 months post-infusion). Furthermore, CTL infusion was associated with a 48.7% overall response rate in patients with active disease, though for the subset of patients with metastatic disease the overall response rate was only 10%.

5. Conclusion

In summary, the anti-EGFR monoclonal antibody, cetuximab, has been associated with a small but significant overall response in patients with recurrent/metastatic disease who progressed despite platinum-based therapy. Furthermore, nearly half of the patients in that study achieved stable disease. Preliminary data in the locally advanced setting are more promising, with one small trial reporting an 83% overall response. In both of these trials, cetuximab was given in combination with platinum-based chemotherapy. Treatment with small molecule inhibitors has been less successful: two studies of the tyrosine kinase inhibitor, gefitinib, have shown no benefit. Inhibitors of angiogenesis are theoretically attractive subjects of investigation given the documented VEGF overexpression in NPC, and these agents warrant further investigation. Finally, the clear association between NPC and EBV represents a disease-specific biologic property that may be exploited via immunotherapy, and early work with EBV-specific cytotoxic T lymphocytes has produced promising results.

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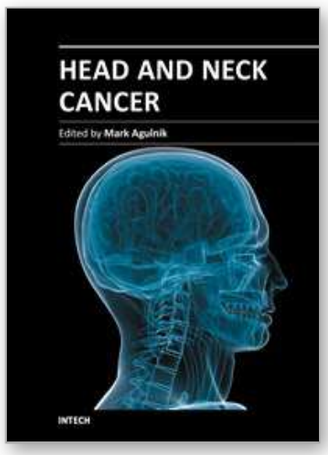

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Head and Neck Cancer provides an interesting and comprehensive overview of all aspects of head and neck cancer including overviews of the disease, basic science aspects pertaining to the disease, diagnosis, treatment and outcomes for patients with this disease. The chapters written by world renowned experts cover the entire discipline of head and neck oncology and include discussions of regional disparity is, advances in basic science understanding, advances in her radiotherapy, chemotherapy and targeted agents as well as a focus on reconstruction, prostheses, and aspects of quality of life and health outcomes. The book is designed to be both practical and comprehensive for every physician treating his complex disease.

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