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Update on Medical Therapies of Nasopharyngeal Carcinoma

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1. Introduction

Nasopharyngeal carcinoma (NPC) is a common head and neck cancer in most of the countries of the Mediterranean Area (MA) and North Africa (NA). Its incidence is variable from <1 in sporadic areas to 2-7/100000 in NA and MA to 20-30/100000 in Southern China and Southeast Asia (Boussen et al,2010; Lee et al, 1992). It's different from other head and neck cancers due to its particular epidemiology, natural history and therapeutic considerations (Boussen et al, 2010; Lee et al, 1992).

It's highly radiosensitive and chemosensitive. Loco-regional radiotherapy (RT) remains the primary treatment for early stage disease (T1-T2, N0, N1), while combined chemotherapy-radiotherapy became the gold therapeutic standard in locally advanced disease i.e T3-T4, N2-N3 (Boussen et al, 2010; Lee et al, 1992; Baujat et al, 2006). Combined treatment leads to a significant improvement on overall and disease-free survivals, but NPC remains at a high metastatic risk, requiring the search for new salvage therapeutic protocols (Boussen et al, 2010; Lee et al, 1992: Xu et al, 2010). This paper will focus on recent data on epidemiology and progresses on medical therapies in NPC.

2. Transitional epidemiology of NPC

NPC represents 2 to 5% of all cancers in males, it is second to laryngeal cancer in most of the Mediterranean countries ant its incidence varying from 1 in Lebanon, Egypt, Greece, Turkey to 2-5/100000 in North Africa (NA), where it's characterized by a bimodal age repartition with a first peak at adolescence (Boussen et al, 2010; Ben Abdallah M, 2010). This high frequency of children and adolescents affected by NPC in Tunisia open the discussion to reach the maximum cure rate with minimal late aftereffects (Boussen et al, 2010). Endemic NPC is highly frequent in south-east Asia with an incidence > 20/100000 compared to NA (Tse et al, 2006). During the last 10 years, authors from Singapore reported a decrease of NPC incidence especially for UCNT type. This epidemiologic transition could be attributed to a socio-economic level increase as well as diet modification, such as salted fish (rich in nitrosamines) consumption decrease (Tse et al, 2006). The same trend have been observed

(Sun et al,2005) from 1992 to 2002 for the incidence Rates of NPC among Chinese Americans Living in Los Angeles County and the San Francisco Metropolitan Area with a decrease of 37% for men by 37% and only 1% in women(7). Conversely, male and female NPC world age-standardized incidence reported to be 27.5/105 and 11.3/105 respectively, seems to be stable from 1970-2007 in the Chinese endemic area of Zhongshan (Wei et al, 2010). In Tunisia (Ben Abdallah M,2010), we are observing, like in Singapore, a decreasing incidence of NPC and a projection from the North Tunisia cancer registry for 2024 suggests a significant drop of NPC incidence, while breast and colon cancer will clearly increase.

3. Staging and classification

During the last 20 years, NPC natural history became more known in term of loco-regional extension as well as metastatic disease with technical improvements of flexible nasofibroscopes and modern imagery, such as magnetic resonance imagery and Pet-scan(Chan et al,2011). This better definition of loco-regional disease extension leads to successive actualizations (1997, 2002 then 2009), of the more used TNM UICC anatomo-clinical classification, more adapted to discriminate between the different T and N prognostic stages and eventually to adjust therapeutic protocols according to risk group (Union for International Cancer Control,2009).

T1 Nasopharynx, oropharynx or nasal cavity (**was T2a***) without parapharyngeal extension

T2 Parapharyngeal extension (**was T2b***)

T2a Tumour extends to oropharynx and/or nasal cavity without parapharyngeal extension

T2b Tumour with parapharyngeal extension

T3 Bony structures of skull base and/or paranasal sinuses

T4 Intracranial, cranial nerves, hypopharynx, orbit, infratemporal fossa/masticator space

N1 Unilateral **cervical**, unilateral or bilateral retropharyngeal lymph nodes, above supraclavicular fossa; < 6 cm

N2 Bilateral **cervical** above supraclavicular fossa; < 6 cm

N3 Metastasis in lymph node(s), >6 cm in dimension (N3a) or in the supraclavicular fossa (N3b)>6 cm

7th TNM classification of UICC (International Union against Cancer, 2009)-AJCC, American Joint Committee on Cancer. *Recent modification

4. Chemotherapy

Systemic chemotherapy (CT) in NPC is indicated because disease is confined to nasopharynx in < 10% of cases (Lee et al; 1992), while parapharyngeal extension, skull base and intracranial involvement are reported in 80% and 25 to 35% and pathologic cervical nodes are present in 75 to 90% of patients, increasing the risk of initial metastases in advanced stages (Lee et al;1992; Sham et al,1991; Teo et al,1992). CT have been used since the eighties in palliative intent with few devoted phase II trials and the most active agents are

cisplatin, 5-fluorouracil (5-FU), doxorubicin, epirubicin, bleomycin, mitoxantrone, methotrexate and vinca alkaloids or more recently ifosfamide or gemcitabine(Bensouda et al,2011;Boussen et al,2010;You et al,2011). CT have been used from the nineties as adjuvant then primary CT(PCT) in NPC(Bachouchi et al,1990) confirming the chemosensitivity of NPC with a high rate of radiologic/endoscopic objective responses to PCT (Bachouchi et al,1990; Ekenel et al,2011).

5. Radiotherapy

RT remains is the mainstay of of NPC treatment due to its radiosensibility (Boussen et al, 2010; Chan et al, 2010; Lee et al, 1992). Loco-regional RT targets primary tumor, its regional extension and both neck sides (levels Ib–V, and retropharyngeal nodes). Consensual dose is around 70 Gy with dose-fractions of 1.8 to 2Gy, indicated for sterilization of bulky tumor volume and 50–60 Gy or 46–60 Gy for areas at high risk (Lee et al, 1992; Chan et al, 2010).

6. Concomitant CT-RT

The results of concurrent chemoradiotherapy (CCRT) Intergroup study 0099, made gradually this combined approach as a standard in the treatment of patients with stage III and IV NPC (Al Sarraf et al, 1998; Chan et al, 2010). Within the randomized other studies, several meta-analysis and a pooled data analysis reported a significant improvement of survival in NPC patients treated by CTRT versus RT alone (Baujat et al, 2006). The NPC meta-analysis had shown the superiority of concomitant scheme vs neoadjuvant chemotherapy. It concerned 1753 patients with N1> 2cm, N2> 3cm, N3, T4, PS 0- 1, WHO 2-3 and a mean age of 46 years. The follow-up was < 5 years for 2 trials (299 pts), 5-9 years for 6 (1454 pts) and a median follow-up of 6 years for the whole population. Delivered radiotherapy were for tumor: 65-74 Gy, for N0 : 50-66 Gy and for N+ 60-76 Gy, by using a "classical" technique and a boost for residual N associated to concomitant cisplatin-based CT in all trials. Authors reported a benefit of concomitant scheme by increasing 5-year OS from 56% to 62% and EFS from 42% to 52% significantly better than neoadjuvant chemotherapy. Recently a meta-analysis focused on South East Asian phase III trials of CT-RT from the NPC endemic area. 1608 patients were collected from seven trials (Zhang L et al, 2010) and they reported Risk ratios (RRs) of 0.63 (95% CI, 0.50 to 0.80), 0.76 (95% CI, 0.61 to 0.93) and 0.74 (95% CI, 0.62 to 0.89) for 2, 3 and 5 years OS respectively in favor of the CCRT group. Concerning the 3-years absolute number of locoregional recurrence rate (LRR), a significant overall benefit in favor of the addition of chemotherapy was found with RR of 0.67 (95% CI, 0.49 to 0.91). A significant decrease of metastatic risk was also observed in term of 3-years absolute number of distant metastasis rate (DMR) with a RR of 0.71. The RRs were larger than that detected in the previously reported meta-analysis (including both endemic and non-endemic), and authors concluded that "the relative benefit of CCRT in endemic population might be less than that from previous meta-analyses".

6.1 CT Protocols of concomitant CT-RT

The schemes used for CTRT are mainly based on "Al Sarraf" schedule with Cisplatin 100mg/m2, every 3 weeks on D1,22,43 or weekly Cisplatin at 40mg/m2(Chan Scheme),

who's the most frequently used in MA and NA, while radiotherapy doses is usually ≥66Gy (1.8-2Gy/Fx/d, 5Fx/wk) for primary nasopharyngeal tumor and its extensions + additional boosts to the parapharyngeal space, the primary or nodal sites not exceeding 20Gy. Since 10 years, CCRT is now recognized and applied as the better therapeutic approach for locally advanced NPC (Al Sarraf,1998 ; Chan et al,2010).

6.2 Acute and late toxicities of CT-RT

CT-RT compared to PCT, however increased significantly acute grade 3-4 toxicity at the end of combined treatment i.e mucositis, radiodermitis, dysphagia and consequently severe weight loss (WL) in most of the open or randomized studies (Table 1). This acute toxicity reduced considerably the compliance of weekly concomitant cisplatin, that was administered during the 6 weeks of CT-Rt in 94%,88%,74%,35%,7% and 3% for weeks 1 to 6 in Hui study (Hui et al,2009). The frequency of severe WL > 5-10% is probably underestimated by many authors and requires sometimes nasal tube feeding or parenteral nutrition as well as delay in the planned protocol. In a Chinese study (Qiu et al, 2011), of patients treated by CT-RT for NPC, 56% had at baseline, a mean 5% WL evaluated at 6.9 Kg after CT-RT (range 2.1-12.6 kg). Xerostomia is one of the most frequent sequelae after salivary gland irradiation and Intensity-Modulated RT permits to reach a high tumor control rate, but also to reduce severity and frequency of xerostomia (Lee et al, 2009).

Author/year	Hui/2010		Lee/2010	Zheng/2010
After PCT	An	---	--	1.7%
	Neutr	97%	--	6.8%
	Thr	--	--	--
	N/V	8.8%	--	5.1%
After CT-RT				
	An	8.8 19.2	19 1	39%
	Neutr	26.4 15.3	32% 1%	35.6%
	Thr		2% 0%	
	Mucos	23.5 7.7	61% 48%	---
	N/V	8.8 7.7	18% 1%	47.1%
	WL		27% 27%	
	Rad		20% 16%	
Late toxicities				
	Dys	--- 3.8%	1% 0%	3.4%
	Xer	32.4 30.8%	--- ---	91.5%
	Skin	11.8 19.2%	4% 5%	
	Subc	20.6 11.5%		
	HL	8.8 11.5%	6% ---	3.4%
	Otit		21 15%	3.5%
	Hypoth		8% 6%	6.8%
	SC	5.9 3.8%		

Table 1. Acute and late toxicities after CT-RT.

Despite many technical advances in RT, late toxicities i.e mainly xerostomia, cervical subcutaneous fibrosis, trismus, hearing loss of less frequently second cancers are observed decreasing the Quality of Life of long-term survivors from NPC, specially those treated in childhood or adolescence (Boussen et al,2010; Xiao et al,2011).

6.3 What next after concomitant CT-RT?

After the era of exclusive CT-RT, appeard the next generation protocols associating PCT followed by CT-RT (Fountzilas et al, 2011, Hui et al, 2009). PCT protocols included "classical" 5FU-cisplatin, anthracyclin-cisplatin or more recently taxanes-cisplatin associations (Table 2). Hui and al, reported their results on 65 patients treated cisplatin-docetaxel (DC) protocol followed by CCRT vs CCRT alone. They observed a significant survival benefit at 2 years for the DC arm (93% vs 76%, p = .013). Others studies including also taxanes, showed a benefit for overall and disease-free survival of patients treated for NPC in MA are currently varying from 66 to 94% and 63 to 88.2% (table 3). Many of these studies have a short Follw-up, but OS and DFS rates seems to be promising probably better than those reported in exclusive CT-RT. In Tunisia, a prospective GORTEC French trial is ongoing, comparing 2 cycles of primary TPF followed by chemoradiotherapy vs CCRT with weekly cisplatin (40mg/m2) in advanced(N2-3, T3-4).

Author/year	Nb	CT	RT	ORPCT	ORCT-RT	OS/DFS
Zheng/2010	60	Ned/FU	IMRT	-----	95.3%	3 yr 85.5/75%
		Ned Conc	70/55-60			
Fountzilas	72	CPE-CRT	66-70/50-66	70%	83%	3 yr 66.6/64.5
2011	69	CRT	--------	-----	85%	3 yr 71.8/63.5
Hui	34	DC-CRT	70/50-60	76,5%	97.1%	3 yr 94.1/88.2%
2009	31	CRT	70/50-60	----	100%	3 yr 69.2/63%

CPE :Cisplatin-Paclitaxel-Epirubicin, DC : Docetaxel-cisplatin, CRT : Concomitant chemo-radiotherapy, Ned : Nedaplatin.

Table 2. Therapeutics results of open or randomized studies of PCT followed by CT-RT.

7. Tumor volume in NPC: A new prognostic factor?

Instead of the classical T,N,Age,Sex and histologic type, prognostic value of Primary Tumor Volume(PTV), measured by CT-scan have been explored for NPC in 112 patients with Stage I-IVB NPC treated by IMRT (Chen et al, 2011). The mean PTV was 33.9 ± 28.7 ml and classified from V1 to V4 (from 15.65 to 50,5ml). It impacted on 5-year overall survival who varies from 88.5, 83.3, 82.4 to 54.5% for V1 to V4 from, showing that V1-V4 are clearly separated from V4 (p = 0.014). Cox proportional hazards regression model analysis showed that a PTV >50 ml was an independent risk factor for radiotherapy (risk ratio = 3.485, P = 0.025). In 56 Turkish patients with locally advanced NPC, PTV have been calculated by measuring tumor diameters by CT and MR film hardcopies computed as an ellipsoid ($V=4/3 \cdot \pi \cdot d1 \cdot d2 \cdot d3$) to obtain the diameter-based volume(Sarisahin et al, 2011). They reported in the monovariate analysis, that primary tumor volume have a significant predictive value on DFS and DMFS, if tumor volume < 20ml, DFS was 60% vs 0% if > 60ml(p=0.007). The residual tumor volume (RTV) at first control after treatment was also

found to be a significant prognostic factor on LRRFS (p=0.03). However Nasopharyngeal PTV alone is missing the volume of satellite cervical nodes that have probably an important prognostic value.

8. Recurrent/metastatic disease

NPC failures are mainly metastatic, to bones, lungs and liver and loco-regional relapses became more rare due to the high loco-regional control rate obtained by loco-regional RT (Leung et al,2005; Cvitkovic et al,1993). In metastatic situations, NPC remains chemosensitive to cisplatin, adriamycin, 5Fluorouracil or more recently taxanes, gemcitabine or oral capecitabine(Boussen et al,1991,2010;You et al,2011;Bensouda et al,2011). Prolonged survival after palliative CT and/or RT could be observed in patients with bone metastases in case of bone MTS only and less than 4 sites involved (Fandi et al,2000;Cao et al,2011). In isolated bone metastases, prolonged responses under biphosphonates plus CT have been also reported, with a significant reduction of skeletal events and better (11.5 vs 5.5 months, $P < 0.001$) progression-free survival and overall survival (23.5 vs. 17.5 months, $P < 0.001$) of combined vs chemotherapy alone group. (Jin et al,2011). Even in case of lung MTS disease, different prognostic groups could be identified according to size and numbers of metastatic nodules (Cao X et al, 2011).

9. Effective screening for NPC?

Some efforts have been done oriented for early detection in relatives of patients considered at high risk for NPC, according to their viral DNA and anti-EBV profile (Baizig et al,2011;Liu et al,2011). Sophisticated endoscopic technique have been also tested to detect easily early stages of NPC (Lin et al,2011, Lin et al,2011).

10. Conclusion

NPC is a very interesting within the other head and neck cancers, occurring in young patients non-smokers/non drinkers and significant improvement of therapeutic results have been reached during the last 30 years, 5 years-OS increasing from 20-30% to more than 75% with the recent protocols of CT-RT or PCT followed by CT-RT that included taxanes (Boussen et al, 2010, Chan et al,2010). Overexpression of EGRF, present in more than 70% of NPC leads to the use of Cetuximab as adjuvant concomitant or maintenance therapy (Yang Y et al, 2011). Anti-angiogenesis therapies like Pazopanib have been also tested without proven efficacy(Lim et al,2011). The significant survival improvement made NPC a more curable disease and efforts were made to reduce late sequelae specially in children and adolescents and to affect minimally quality of life after combined chemo-radiotherapy (Fang et al,2011;Marucci et al,2011;Shueng et al,2011).

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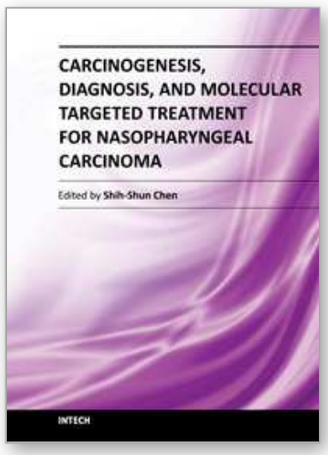

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This book is a comprehensive treatise of the potential risk factors associated with NPC development, the tools employed in the diagnosis and detection of NPC, the concepts behind NPC patients who develop neuro-endocrine abnormalities and ear-related complications after radiotherapy and chemotherapy, the molecular mechanisms leading to NPC carcinogenesis, and the potential therapeutic molecular targets for NPC.

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