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ORIGINAL ARTICLE

Induction chemotherapy with carboplatin and taxol followed by radiotherapy and concurrent weekly carboplatin + taxol in locally advanced nasopharyngeal carcinoma

Mario Airoldi · Pietro Gabriele · Anna Maria Gabriele · Massimiliano Garzaro · Luca Raimondo · Fulvia Pedani · Fabio Beatrice · Giancarlo Pecorari · Carlo Giordano

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Abstract
Purpose Aim of this study was the clinical evaluation of carboplatin–taxol combination in a neoadjuvant and concomitant setting with conventional radiotherapy in loco-regionally advanced nasopharyngeal carcinoma (A-NPC).
Methods Thirty patients were treated with three cycles of carboplatin (AUC6) plus taxol (175 mg/m^2) on day 1 every 3 weeks, followed by weekly carboplatin (AUC1) plus Taxol (60 mg/m2) and concomitant radiotherapy (70 Gy).
Results We observed the objective complete response rates of 33% (after chemotherapy) and 87% (after chemo-radiotherapy). Treatment tolerability and toxicity were controllable. Three- and five-year progression-free survival were 80 and 75%, respectively, and 3- and 5-year overall survival were 85 and 80% (follow-up 49.5 months). Five-year loco-regional control was 90.3%, and five-year distant metastases–free survival was 85%.
Conclusions Neoadjuvant chemotherapy with such protocol represents a feasible, efficient treatment for patients with A-NPC, ensuring excellent loco-regional disease control and overall survival with low incidence of distant metastases.

Keywords Nasopharyngeal carcinoma · Neoadjuvant chemotherapy · Chemoradiation · Carboplatin · Taxol

M. Airoldi · F. Pedani
Department of Medical Oncology,
San Giovanni Battista Hospital, Turin, Italy

P. Gabriele
Radiation Therapy Division, Cancer Institute,
Candiolo, Turin, Italy

A. M. Gabriele
Radiation Therapy Division,
San Giovanni Antica Sede Hospital, Turin, Italy

M. Garzaro (✉) · L. Raimondo · G. Pecorari · C. Giordano
1st ENT Division, Department of Clinical Physiopathology,
University of Turin, San Giovanni Battista Hospital,
Via Genova, 3, 10126 Turin, Italy
e-mail: garz@libero.it

F. Beatrice
ENT Department, Giovanni Bosco Hospital, Turin, Italy

Introduction

In nasopharyngeal carcinoma (NPC), the place of chemotherapy (CHT), which is not discussed in metastatic disease, is controversial for the initial management of the disease.

Recent trials and meta-analyses highlight the need to associate chemotherapy with radiotherapy (RT): concomitant chemo-radiotherapy (CRT) appears to be now the standard treatment for locally advanced (T2B and more) and/or node positive (N+) patients [1].

Despite its more questionable role, the addition of induction CHT remains attractive in loco-regionally advanced NPC patients, partly with the purpose of shrinking down the primary tumour before irradiation and partly in order to eradicate micrometastases without delay. However, phase III trials, comparing induction chemotherapy with radiotherapy alone [2–5], failed to show an improvement in overall survival, despite a significant reduction in local and distant failures.

Four recent published studies [6–8], performed in extra-European countries, shown that induction CHT followed by CRT obtained high responses in patients coming from both endemic and non-endemic areas: in two trials, the

authors proposed a three-drug induction scheme, while in the others cisplatin + epirubicin or paclitaxel and carboplatin were, respectively, administered.

We have published our previous experience with induction cisplatin plus epirubicin followed by conventional radiotherapy plus every 3-week cisplatin administration [9]; our results confirm the high activity of this approach in a non-endemic population.

No phase II trials have investigated a two-drug combination during conventional, non-splitted, radiotherapy after a full course of induction chemotherapy.

When the study was designed, the association carboplatin + taxol was known as a feasible and effective combination in advanced metastatic nasopharyngeal tumours [10–12].

These two drugs were known as radiosensitizers, and weekly taxol infusion was indicated as an ideal way to give dose density with enhanced therapeutic index [13].

In this paper, we report our experience with neoadjuvant chemotherapy with carboplatin + taxol followed by radiotherapy with weekly carboplatin–taxol combination in locally advanced NPC, observed in a non-endemic population.

Methods and materials

Eligibility

In the present multicentric retrospective analysis, patients having histological confirmed NPC, stage III-IVB according to 2010 AJCC stage classification (7th ed.), who had received no previous CHT and/or RT were included. Individuals aged >18 presenting measurable disease and WHO performance status (WHO-PS) of 0 or 1 were also considered eligible for our study. Clinical introduction of this two-drug association was approved by the Ethics Committee of each participating centre and all patients provided written informed consent.

Patients were excluded in case of inadequate organ function, as indicated by an absolute neutrophil count $\leq 1.5 \times 10^9$/L, platelet count $\leq 100 \times 10^9$/L, serum creatinine ≥1.5 times the upper limit of normal or 24-h creatinine clearance ≤50 ml/min, serum bilirubin >1.5 times the upper limit of normal (ULN), ALT, AST and alkaline phosphatase levels ≥2 times the ULN. Moreover, we considered not eligible patients presenting prior malignancy apart from non-melanoma skin cancer or carcinoma in situ of the uterine cervix, pre-existing motor or sensory neurotoxicity ≥ WHO grade 2, significant hearing impairment unless due to NPC, active uncontrolled infection, unstable cardiac disease and pregnancy or lactation. Written informed consent was obtained from all patients.

Evaluation and follow-up

The main contents of pretreatment evaluation have been the following: physical examination, assessment of PS, urine analysis, complete blood cell count (CBC) with differential, serum electrolytes, liver function tests, magnetic resonance and measurement of index lesions. Other tests included electrocardiography (ECG) and 24-h creatinine clearance. Baseline imaging was composed by bone scan, contrast-enhanced computed tomography (CT) scan of thorax and abdomen, CT and/or magnetic resonance imaging (MRI) of the nasopharynx and neck.

During the treatment period, patients underwent weekly physical examination and toxicity assessment. Laboratory examinations and 24-h creatinine clearance had to be repeated every 3 weeks, while CBC count had to be performed on days 1 and 8 of each cycle of neoadjuvant chemotherapy and once a week during RT.

Assessment of tumour response by clinical examination and head and neck MRI or CT was performed after neoadjuvant CHT. Once completed CHT and CRT, endoscopy, head and neck MRI or CT, thoracic and abdominal CT scan could be performed.

Six to eight weeks after the completion of CRT, complete physical examination, nasopharyngoscopy, thoracic and abdominal CT scan, MRI of nasopharynx, biochemistry and blood cell count could be performed. Patients had to be followed up by clinical examination every 2 months during the first year, every 3 months for the subsequent 2 years and every 6 months thereafter. Nasopharyngoscopy and imaging (CT, MRI or ultrasound investigation) were disposed for patients developing signs or symptoms suggestive of disease recurrence. Endoscopic or ultrasound guided biopsy had to be performed, if deemed necessary.

Tumour response was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria. Systemic toxicity from treatment was graded according to WHO and Radiation Therapy Oncology Group (RTOG) criteria.

Induction chemotherapy

Neoadjuvant CHT consisted of 3 cycles of paclitaxel 175 mg/m2 administered over 3 h followed by carboplatin area under the concentration–time curve 6 (carboplatin dosing to the area under the curve of 6 was calculated using Calvert formula) administered over 30–60 min, repeated on day 22. Paclitaxel was preceded by premedication with dexametasone (20 mg), diphenidramine (25 mg) and ranitidine (50 mg). If the absolute neutrophil count was less 1,200/mm3 or platelets was less than 100,000/mm3 on day 22, treatment was held until counts returned to this level. If the cycle was held more than 3 weeks, patients

proceeded to tumour response evaluation and started chemo-radiotherapy. Prophylactic use of recombinant granulocyte colony-stimulating factor was not allowed.

Concurrent chemo-radiotherapy

Chemotherapy consisted of 60 mg/m2 of paclitaxel given over 1 h intravenously every week. Patients were pre-treated with dexametasone 20 mg given orally on the evening prior to and the morning of paclitaxel infusion. Diphenidramine 25 mg and ranitidine 50 mg were given iv prior to paclitaxel infusion. Carboplatin was given after paclitaxel infusion, for 30–60 min. Carboplatin dosing to the area under the curve of 1 was calculated using Calvert formula. Antiemetics were administered as the routine practice. Colony-stimulating factors were not used.

Dose modification for toxicity

Toxicity was graded according to the WHO Criteria. Chemotherapy dose modifications were made for grade 3–4 mucositis or mucositis requiring hospitalization for hydration/pain management or for grade 3–4 haematologic toxicity. If grade 4 mucositis occurred, chemotherapy was withheld and resumed after the mucositis improved to $\leq$grade 2. Carboplatin was withheld if a second episode occurred, and both paclitaxel and carboplatin were withheld if a third episode occurred.

For haematologic toxicity, the dose of paclitaxel and carboplatin was reduced to 50% for granulocyte count of 500–1000/μL and/or platelet count of 50,000–75,000/μL. Both drugs were withheld if the granulocyte and/or platelet levels dropped below 500/μL and 50,000/μL, respectively. Colony-stimulating factors were not used. If the weekly granulocyte count was <500/μL, or platelet was <50,000/μL, radiotherapy was withheld until counts, measured twice weekly, recovered to above that level.

Enteral tube feeding was used following physician's prescriptions.

Radiotherapy

Radiation treatment was started 3 weeks after the three cycles of neoadjuvant chemotherapy (NACT). Three-dimensional conformal radiotherapy (3D-CRT) was performed on all patients.

Treatment was done using 6 MV photons on a Siemens Primus Linear Accelerator with a multileaf collimator.

For head immobilization in the supine position, a thermoplastic facial mask (MED-TEC) was used.

CT scans were performed for treatment planning.

The clinical target volume (CTV) and organs at risk (OaRs) were outlined on the axial images and were determined according to the CT/RMI findings of the gross tumour and microscopic extension. A 10-mm expansion margin was applied to the CTV to obtain the planning target volume (PTV).

The CT images were transferred to the PLATO-Nucletron Planning System, which allowed to obtain digitally reconstructed radiographs (DRR) from the digital image set.

Planned RT consisted of 70 Gy, in 35 fractions, over 7 weeks to all known sites of disease and 50 Gy to sites of potential spread, including the uninvolved neck.

Residual cervical lymphoadenopathy was supplemented with electron beams.

For the first 40 Gy, the nasopharyngeal area and the upper neck were irradiated in one volume with conformal lateral opposing fields. An anterior field was used for the lower neck and supraclavicular fossa with a laryngeal block.

Thereafter, in 18 cases, the radiation beams were rearranged to shrink the field size progressively, after every 10 Gy, to establish gradually a 100% isodose level that covered the PTV with a total actual dose of 70 Gy.

In 12 patients, in order to reach maximal conformity, after the first 40 Gy of treatment, we employed 5–7 fields for the nasopharyngeal region.

The beam arrangements were determined depending on the anatomical features of the tumour and its relationship with surrounding structures. Wedges were used to improve the conformity of the isodose curves, when necessary.

Maximal doses to the optic pathways, brain stem and spinal cord were limited to 50 Gy, 54 and 45 Gy, respectively.

For all patients and treatment plans, dose–volume histograms (DVHs) were calculated for the PTV and OaRs.

Treatment verification was obtained with portal imaging for each new field and repeated weekly.

Treatment interruptions were only allowed for severe normal tissue reactions, such as confluent mucositis.

Statistical methods

Objective response rate (ORR) represented the primary endpoint, and it could be defined as the proportion of patients whose best response was either partial or complete (PR + CR).

Secondary endpoints included disease control rate (DCR), defined as the proportion of patients whose best response was either PR or CR or stable disease (SD), occurrence of grade 3–4 adverse events, as well as progression-free survival (PFS) and overall survival (OS).

PFS definition was as follows: the time from the date of the study entry up to the date of first progression, second primary malignancy or death from any causes, whichever

came first. Subjects not progressed or died at the time of the analysis were censored at the last disease assessment date. OS was defined as the time from the date of the study entry to the date of death from any cause. Subjects who were not reported as dead at the time of the analysis were censored at the date they were last known to be alive. Survival curves were estimated using the Kaplan–Meier method.

All enrolled patients meeting the above described eligibility criteria and not presenting major violations within the duration of our study became subjects of the analysis. Such analysis, indeed, was restricted to patients who received at least one cycle of either induction CHT or CRT.

Results are expressed as point estimates and their 95% confidence intervals (95% CIs). Analysis was carried out using SAS Software, version 9.1 (SAS Institute, Cary, NC).

Results

From 2002 to 2007, 62 patients, affected by NPC, have been observed in the participating centres; 30 patients were enrolled in this study protocol. Twenty-two (73.3%) patients were men and 8 patients were women (26.7%) with a median age of 54 years (range 29–69). ECOG performance status was 0 in 27 patients (90%) and 1 in 3 patients (10%). WHO histology was as follows: type 2 histology in 3 patients (10%) and type 3 in 27 patients (90%). Positive tissue EBV DNA was observed in 23 patients (76%). According to the 2010 AJCC staging system, 14 patients had stage III (47%), 13 patients stage IVa (43%) and 3 patients stage IV b (10%) disease; $T_{3–4}$ lesions were 25/30 (83.3%), while N2/3 lesions were 21/30 (70%) (Table 1). Local extension outside nasopharyngeal cavity was as follows: bone lysis in 7 patients (23.3%), paranasal sinuses involvement in 3 patients (10%), infratemporal fossa extension in 6 patients (20%) and intracranial extension in 9 cases (30%).

Activity

All 30 patients completed the planned treatment without protocol violations, and therefore, they all were considered assessable for response. After two cycles of CHT, no clinical progression was registered and all patients completed the third cycle. After three cycles of neoadjuvant CHT, we registered the following results: 10 patients (33%) achieved clinical and imaging complete response (CR); eighteen patients (60%) had a partial response (PR); 6 patients (20%) achieved PR on the tumour site (T) and no change in regional lymph nodes (N); twelve patients (40%) achieved a PR on T and N; two patients (6.6%) had no change neither in T nor in N site. Objective response rate was 93% (95% CI 78.4–98.8%), while disease control rate was 100% (95% CI 94.1–100%).

At the end of CRT, 26 patients (87%) achieved a clinical CR at both T and regional node and 4 patients (13%) were in PR (2 patients on T and N, 1 patient on T only and 1 patient on N only) for an overall response rate of 100% patients. Objective response rate was 100% (95% CI 89.1–100%).

Follow-up at 12 weeks confirmed that 26 patients (87%) had reached a CR and that 4 patients (13%) were in PR according to imaging techniques. One patient with partial response in the neck was submitted to bilateral neck dissection achieving a complete remission.

At a median follow-up time of 49.5 months (range 16–89 months), 6 (20%) patients progressed and 4 (13.3%) died of tumour. The 3- and 5-year PFS were 80% (95% CI 69–99%) and 75.0% (95% CI 55–85%), respectively, and the 3- and 5-year OS were 85.0% (95% CI 69–92%) and 80.0% (95% CI 66–91%) respectively (Fig. 1). There was a non-significant PFS and OS difference between stages III and IV lesions ($P > 0.05$).

Five-year loco-regional control was 90.3% (95% CI 69–99%), and five-year distant metastases–free survival was 85% (95% CI 72–97%) (Fig. 2).

In the follow-up, a progression was found in 6 patients and, in particular, two patients had T relapse, one had T and N recurrence, three developed distant metastases. All patients (3 cases; median time to metastases = 30 months; range 18–36) with distant metastases (lung 2, lung + bone 1) died after a median period of 27 months (range 21–39 months); they were treated with a median of 2 lines of chemotherapy (range 1–4). T relapses (median time to relapse = 19 months) were treated with re-irradiation plus chemotherapy achieving a persistent complete remission. One patient with T and N relapse was treated with chemotherapy achieving a PR. The second-line chemotherapy was cisplatin plus epirubicin in all cases.

Toxicity

A list of acute toxicities with reference to WHO criteria is reported in Tables 2 and 3.

Table 1 Tumour stage versus Node stage (AJCC Staging 2010)

	T1	T2	T3	T4	Total
N0	–	–	1	8	9
N1	–	–	0	0	0
N2	3	1	9	5	18
N3[a]	1	–	–	2	3
Total	3	2	10	15	30

[a] All patients were N3a

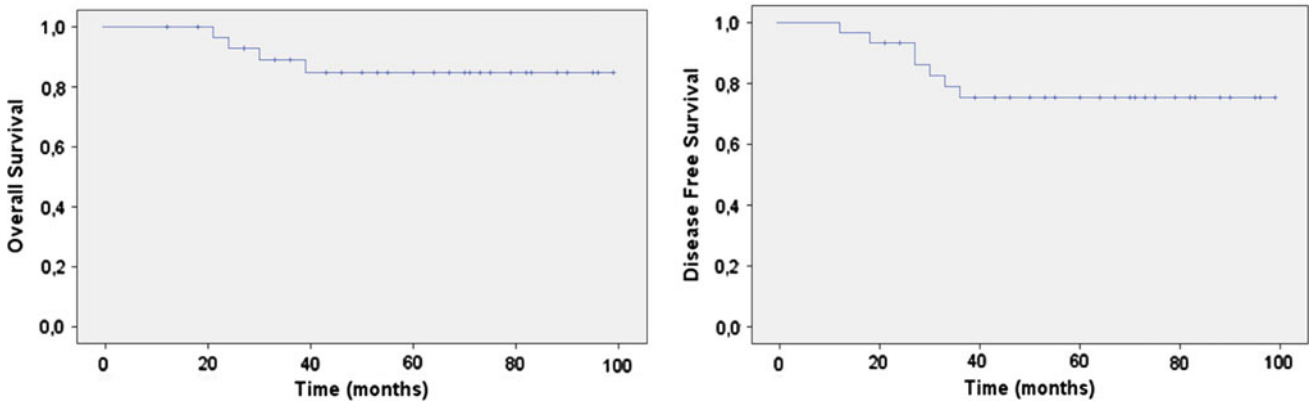

Fig. 1 Overall survival (OS) and disease-free survival (PFS)—30 patients with a median follow-up of 49.5 months

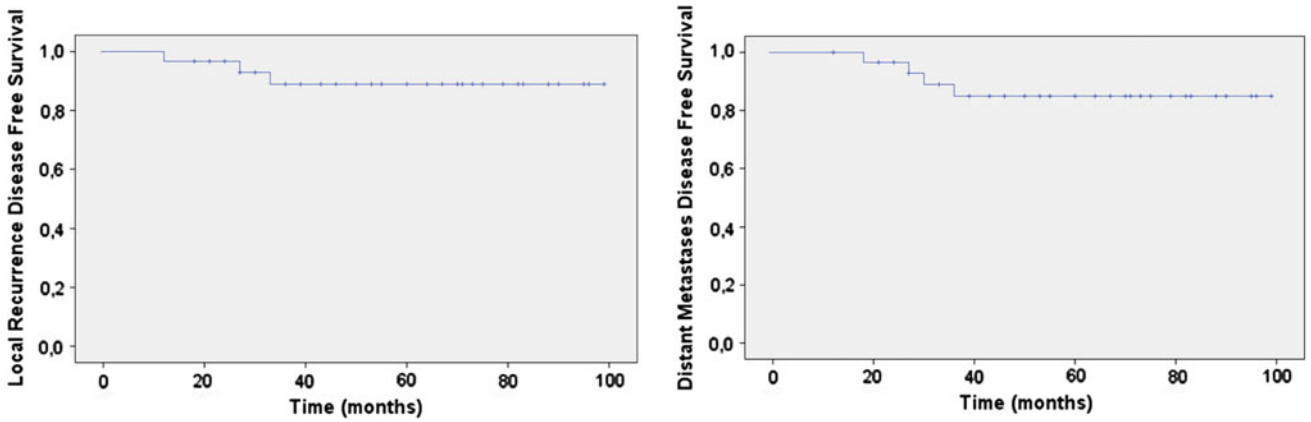

Fig. 2 Local recurrence disease-free survival (LRDFS) and distant metastases disease-free survival (DMDFS)—30 patients with a median follow-up of 49.5 months

Table 2 Acute toxicity (WHO criteria), maximum toxicity per patient during induction CHT

WHO grade	0	1–2	3	4
Neutropenia*	0 (0%)	5 (16.7%)	10 (33.3%)	15 (50%)
Thrombocytopenia	2 (6.6%)	24 (80.0%)	4 (13.3%)	0 (0%)
Anaemia	2 (6.6%)	15 (50.0%)	3 (10.0%)	0 (0%)
Nausea/Vomiting	15 (50.0%)	15 (50.0%)	0 (0%)	0 (0%)
Anorexia	23 (76.7%)	7 (23.3%)	0 (0%)	0 (0%)
Oropharyngeal Mucositis	21 (70.0%)	7 (23.3%)	2 (6.6%)	0 (0%)
Alopecia	6 (20%)	24 (80.0%)		
Skin	0 (0%)	–	–	–
Cardiotoxicity	0 (0%)	–	–	–
Renal toxicity	0 (0%)	–	–	–
Neurotoxicity	0 (0%)	–	–	–
Weight loss	36 (87.7%)	4 (13.3%)	–	–

* Febrile neutropenia in no patient

The most clinical relevant side effect of NACT was haematologic toxicity; grade 3–4 neutropenia was observed in 25 cases (83%) with grade 4 in 15 patients (50%) without any episode of febrile neutropenia. G-CSF was administered to 6 patients (20%). Grade 3 thrombocytopenia occurred in 4 patients (13.3%) without any haemorrhagic episode, while grade 3 anaemia was observed in 3 patients (10%).

The G 3 non-haematologic toxicity was represented only by oropharyngeal mucositis in 2 patients (6.6%). All patients received 3 full-dose cycles of CHT.

The most frequent toxicity during CRT was oropharyngeal mucositis occurring in all cases; 16 patients (53.3%) developed G3 toxicity and 5 (16.6%) had G4 toxicity. Five of them (16.6%) required admission to hospital for intravenous hydration and nasal gastric tube feeding. Grade 3–4 haematological toxicity during CRT was as follows: neutropenia in 19 patients (63.3%; grade 4 in 5 cases—16.6%), thrombocytopenia in 5 (16.6%) and anaemia in 5 (16.6%). No febrile neutropenia or haemorrhagic episode was seen. During CRT, renal toxicity and neurotoxicity were mild, and only 3 patients (10%) developed grade 3 neuropathy, which was treated with gabapentin and resolved in 3 months. In 5 patients

Table 3 Acute toxicity (WHO criteria), maximum toxicity per patient, during CRT

WHO grade	0	1–2	3	4
Neutropenia	0 (.0%)	11 (36.6%)	16 (53.3%)	3 (10%)
Thrombocytopenia	10 (33.3%)	17 (56.6%)	3 (10%)	0 (0%)
Anaemia	8 (26.6%)	17 (56.6%)	5 (16.6%)	0 (0%)
Nausea/vomiting	18 (60.0%)	12 (40.0%)	0 (0%)	0 (0%)
Oropharyngeal Mucositis	0 (0%)	9 (30%)	16 (53.3%)	5 (16.6%)
Alopecia	6 (20%)	24 (80%)		
Skin	2 (6.6%)	21 (70.0%)	7 (23.3%)	0 (0%)
Cardiotoxicity	30 (100%)	–	–	
Renal toxicity	28 (93.3%)	2 (6.6%)	–	
Neurotoxicity	12 (40%)	15 (50%)	3 (10%)	0 (0%)
Weight loss	32 (80.0%)	8 (20.0%)	5 (16.6%)	0 (0%)
NGT	Yes 5 pts (16.6%)			

(16.6%), weight loss was significant and they lost $\geq$10% of their body weight. No toxic deaths were registered during or immediately after treatment.

Twenty-seven patients (90%) received a dose between 66 and 70 Gy; only 3 patients (10%) interrupted radiation therapy for more than 5 days.

During radiotherapy, 189 out of 210 scheduled cycles (90%) were administered: 21 patients (70%) received 7 cycles, 2 patients (6.6%) 6 cycles, 2 patients (6.6%) 5 cycles and 5 patients (16.6%) 4 cycles; the relative dose intensity of taxol and carboplatin was 80.1 and 74.4%, respectively.

We registered mild late side effects and sequelae due to CRT according to RTOG criteria. Neck fibrosis was present in 15 patients (50%) after 6 months of follow-up but it did not take to a relevant clinical problem. RTOG grade 2 xerostomy and disgeusia persisted in 6 patients (20%) during the first year of follow-up and in 3 patients (10%) thereafter. Transient swallowing disorders were reported in 3 (10%) patients. We observed sensorineural hearing loss in 2 (6.6%) patients from the beginning of CRT. Such side effect improved slowly after 1 year from the end of CRT in 1 patient, while it was irreversible in one patient.

Discussion

In NPC, despite the advances made in clinical therapies of curative RT, with or without concurrent CHT, the 5-year overall survival rates of $\sim$75% underscore opportunities for improvement, in particular for patients with advanced disease when survival rates decline to <60% [14].

The results of the last meta-analysis [15] confirm the role of concurrent chemoradiotherapy as a standard treatment for loco-regionally advanced NPC.

A significant benefit was found for overall survival (6% at 5 years) and event-free survival (10% at 5 years) with the addition of chemotherapy. The benefit on survival was essentially observed when chemotherapy was administered concomitantly with radiotherapy.

Induction chemotherapy delivered before radiotherapy is an attractive strategy in patients with NPC. However, phase III trials, comparing induction chemotherapy with radiotherapy alone [2–5], failed to show an improvement in overall survival, despite a significant reduction in local and distant failures.

In a report of pooled data of two prospective randomized trials [16], the use of induction CHT resulted in a 5.4% improvement in disease-specific survival rate ($P = 0.029$) at 5 years, while no significant difference was found in the overall survival rates.

Two randomized studies on the use of NACT showed positive results. The VUMCA I study [2] showed significant reduction in both local and distant failures after chemotherapy. Ma et al. [4] also demonstrated significant improvement in local control after NACT.

Hareyama noted that the use of NACT did not result in a significant improvement in disease-free or overall survival, but there was a positive tendency in favour of the NACT for distant metastasis–free survival [5]. The negative study by Chan et al. [17] is limited by its low power, since it included only 77 patients. Although the overall results of the Asian-Oceanian Clinical Oncology Association (AOCOA) study are negative [3], an unplanned subgroup analysis showed significant improvement in local control among 53 patients with very large nodes.

Five recently published studies [6–9] have shown that induction CHT followed by CRT obtained high responses in patients coming from both endemic and non-endemic areas: in two trials, the authors proposed a three-drug induction

scheme, while in the others cisplatin + epirubicin or paclitaxel and carboplatin were, respectively, administered.

In four out of five trials, the drug administered during radiotherapy was cisplatin alone; only in Oh paper [6], a two-drug combination of 5-fluorouracil and hydroxyurea is administered with once-daily radiotherapy on a week-on week-off schedule.

Our clinical post-CRT CR rate (87%) is good even if it is probably overestimated unless the radiologists examined serial CT images or the ENT performed multiple biopsies from the tumour area. Our PFS and OS results are superimposable to the most favourable of these four papers [7, 8, 18], conforming the high activity of NACT + CRT even in a non-endemic population.

Our neoadjuvant scheme has achieved a percentage of CR (33%) similar to the one reported by our group with a cisplatin + epirubicin combination [9] in a superimposable group of patients. Probably, the two-drug administration during RT has given more myelotoxicity and mucositis even if a direct comparison cannot be done. We chose carboplatin instead of cisplatin with the aim of reducing acute toxicity. In a recent paper, weekly carboplatin gave less anaemia, renal toxicity, mucositis and weight loss in comparison with 3-weekly cisplatin administration [19].

Severe nausea/vomiting was less frequent in carboplatin + taxol group (0% vs 12.5%). Late toxicity was superimposable in our two series.

Our percentage of distant metastases is quite low (10%) even if it is possible to suppose that an induction CHT with three-drug scheme or a molecular targeted therapy integration may improve these results, as reported in other head and neck tumours, different from nasopharyngeal region; however, such observation needs to be evidenced by mean of future randomized trials.

According to our previously reported experience in a very similar series [9], we can draw the following conclusions:

1. NACT with carboplatin and taxol is very well tolerated with a clinical impact superimposable to cisplatin + epirubicin;
2. A two-drug combination during conventional radiotherapy is a feasible treatment with a good compliance, an high relative dose intensity and no significant life-threatening toxicity;
3. A two-drug combination during radiotherapy has an higher acute severe toxicity (neutropenia, anaemia, oropharyngeal mucositis, weight loss) compared to cisplatin every three weeks;
4. Tumour recurrence can be effectively treated with re-irradiation + CHT, obtaining long-lasting complete remissions: this is in accordance with recent reports [20–22].

Although the small series hereby presented, NACT with carboplatin + taxol followed by concomitant weekly carboplatin + taxol + conventional radiotherapy seems to be a safe and effective treatment for a non-endemic population affected by loco-regional advanced NPC; however, this approach needs further phase 3 trials.

Conflict of interest statement All authors disclose any financial and personal relationships with people or organisations that could influence their work.

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