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TPF induction chemotherapy followed by concurrent chemoradiotherapy for locally advanced nasopharyngeal carcinoma: Long term results of a Tunisian series

Résultats à long terme de la chimiothérapie première par TPF suivie de chimioradiothérapie concomitante pour des cancers du cavum localement évolués

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ABSTRACT

Purpose. – We represent in this study the long term results of docetaxel, cisplatin and 5-fluorouracil induction chemotherapy followed by concurrent chemoradiotherapy in Tunisian patients with locally advanced nasopharyngeal carcinoma. The objective of our study is to analyse the efficacy as well as the toxicity of this therapeutic protocol.
Patients and methods. – Between January 2004 and December 2008, 32 patients with locoregional advanced non metastatic disease (T2b or above and/or N1 or above AJCC 2002) were treated in our institution by three cycles of docetaxel, cisplatin and 5-fluorouracil induction chemotherapy every 21 days followed by concurrent chemoradiotherapy. Conventional radiotherapy was delivered using a cobalt 60 machine during 7 weeks with weekly cisplatin (40 mg/m^2).
Results. – Twenty-nine patients (90%) had presented an objective clinical response in lymph nodes after neoadjuvant chemotherapy, with a complete response in 28%. Acute toxicity of docetaxel, cisplatin and 5-fluorouracil induction chemotherapy was dominated by vomiting (59%), asthenia (40.6%), diarrhea (34.4%) and febrile neutropenia (15.6%). The complete response rate after the end of treatment was around 80%. The 5 years overall survival and disease-free survival were respectively 68.2% and 67.5%.
Conclusion. – Our results, in this field of study, are encouraging with acceptable toxicity despite the lack of intensity-modulated radiotherapy technique in our institution during the period of study.

Mots clés :
Cancer nasopharyngé
Chimiothérapie
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RÉSUMÉ

Introduction. – Le traitement standard des cancers du cavum localement évolués est basé sur la chimio-radiothérapie concomitante. Cependant, le taux de rechute locale est de 15 % et celui à distance de 30 %. L'objectif de ce travail était d'étudier les résultats à long terme de la chimiothérapie néoadjuvante par l'association de taxotère, cisplatine et 5-fluoro-uracile, suivie d'une chimioradiothérapie concomitante.
Patients et méthodes. – Il s'agit d'une étude rétrospective rassemblant 32 patients atteints de cancer du cavum pris en charge par le comité des cancers ORL de l'hôpital Habib-Bourguiba à Sfax entre janvier 2004 et janvier 2009. Le suivi médian était de 7 ans (extrêmes : 6–9 ans).

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Résultats. – Vingt-neuf cancers (90 %) ont présenté une réponse clinique objective dans les ganglions lymphatiques après chimiothérapie néoadjuvante, avec une réponse complète dans 28 %. La toxicité aiguë après la chimiothérapie par l'association de taxotère, cisplatine et 5-fluoro-uracile a été dominée par des vomissements (59 %), une asthénie (40,6 %), une diarrhée (34,4 %) et une neutropénie fébrile (15,6 %). Le taux de réponse complète après la fin du traitement était d'environ 80 %. La probabilité de survie globale à 5 ans et celle de survie sans maladie étaient respectivement de 68,2 % et 67,5 %.
Conclusion. – Afin d'améliorer les résultats thérapeutiques, l'une des voies à explorer était d'associer une chimiothérapie néoadjuvante à la chimioradiothérapie concomitante. Nos résultats sur le plan efficacité étaient encourageants comparativement aux données de la littérature, malgré l'absence de la modulation d'intensité durant la période d'étude.

1. Introduction

Nasopharyngeal carcinoma is the second head and neck cancer in Tunisia, with a bimodal distribution according to age [1,2]. About 70% of Tunisian patients were diagnosed with locally advanced tumors (T3-T4, N2-N3) [3]. Exclusive radiotherapy represented the standard of care of nasopharyngeal carcinoma for many years. However, therapeutic results, especially for locally advanced disease, were poor with a high rate of both locoregional relapses and distant metastasis [4,33]. To improve therapeutic results several combinations of chemotherapy and radiotherapy were studied. Induction chemotherapy followed by radiotherapy has enhanced disease free survival without any benefit in term of overall survival [5]. Concomitant chemoradiotherapy is currently the gold standard treatment for locoregional advanced nasopharyngeal carcinoma based on the results of different randomized trials and meta-analysis comparing chemoradiotherapy to radiotherapy alone [6–8]. However, therapeutic results remained unsatisfactory with a high rate of distant metastasis especially in patients with bulky nodal disease. To improve therapeutic results, induction chemotherapy followed by concomitant chemoradiotherapy was analysed in many retrospective and phase II studies [9–11] based on the positive results of the association of docetaxel, cisplatin and 5-fluorouracil (TPF) induction chemotherapy in many phases III trials about patients with locally advanced head and neck cancer [12–14]. In our centre, treatment of patients with locally advanced nasopharyngeal carcinoma has evolved through the time from induction chemotherapy followed by conventional radiotherapy to bifractionnated radiotherapy with or without induction chemotherapy to concomitant chemoradiotherapy and then to induction chemotherapy followed by concomitant chemoradiotherapy [3,15–17]. We represent in this study the long-term results of TPF neoadjuvant chemotherapy followed by concomitant chemoradiotherapy in Tunisian patients with locally advanced nasopharyngeal carcinoma.

2. Materials and methods

2.1. Patients' characteristics

Between January 2004 and December 2008, 32 patients with locoregional advanced non-metastatic nasopharyngeal carcinoma (T2b or above and/or N1 or above AJCC 2002) were treated in our institution. The median age was 42.2 years (range: 18–66 years) and the sex ratio was 2.2. Histological diagnosis was made according to the World Health Organization (WHO) classification. Twenty-eight patients (87.5%) had an undifferentiated nasopharyngeal carcinoma (WHO type 3) and four patients (12.5%) had a poorly differentiated carcinoma (WHO type 2). The staging was according to the American Joint Committee on Cancer – International Union Against Cancer (AJCC – UICC) 2002 TNM classification and included clinical examination of the head and neck region, endoscopy of nasopharynx, computed tomography (CT) or MRI of the head and neck, chest X-ray, abdominal ultrasonography and bone scan (Table 1).

Table 1
TPF induction chemotherapy followed by concurrent chemoradiotherapy for locally advanced nasopharyngeal carcinoma: long term results of a Tunisian series ($n = 32$). T and N classification of the studied population according to locoregional lymph node and tumor extension, based on the American Joint Committee on Cancer – International Union Against Cancer (AJCC – UICC) 2002 TNM classification.

	N					Total	Percentage
	N0	N1	N2	N3a	N3b		
T							
T1	0	0	1	0	1	2	6.2
T2	0	2	5	2	2	11	34.3
T3	1	1	1	5	0	8	25
T4	0	3	5	2	1	11	34.3
Total	1	6	12	9	4	32	100
Percentage	3.1	18.7	37.5	28.1	12.5	100	

2.2. Treatment

Treatment consisted of three cycles of induction chemotherapy every 21 days including docetaxel (75 mg/m^2) on day 1, cisplatin (75 mg/m^2) on day 1 and continuous infusion of 5-fluorouracil (750 mg/m^2 daily for 5 days). During radiotherapy, seven cycles of weekly cisplatin (40 mg/m^2) were administrated. The use of an antibioprophylaxis and primary prophylaxis with granulocyte colony-stimulating factor (GCSF) was not systematic. Radiotherapy was delivered using a cobalt-60 machine. Patients received conventional radiotherapy in 7 weeks. It was given 5 days a week with 2 Gy per day to achieve a total dose of 70 Gy to the nasopharynx and involved neck areas and 50 Gy to the remaining N0 cervical areas. The guidelines for irradiation were as follows: two laterally opposed fields were used to treat the nasopharynx and the upper neck and an anterior cervical field was used to treat the lower neck up to 44 Gy. The remainder dose of irradiation was delivered via an anterior nasal field which included the nasopharynx and all cervical nodes with spinal cord shielding.

2.3. Follow-up and response evaluation

Before each cycle of chemotherapy, clinical conditions, regional lymph node status, blood count and renal function, toxicities and patient complains were evaluated. Treatment response was assessed after the third cycle of chemotherapy by a head and neck examination and 3 months after the end of radiotherapy by head and neck examination, nasopharyngeal biopsy and computed tomography or MRI of the nasopharynx. In addition to the tumor

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