527 Neoadjuvant Docetaxel and Cisplatinum in Locally Advanced Undifferentiated Nasopharyngeal Carcinoma: A Phase II International Study

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ABSTRACT*

Background: Nasopharyngeal carcinoma (NPC) incidence is low in most of the world, but is high in some ethnic groups and geographic areas. Intermediate incidence is seen in North Africa where undifferentiated nasopharyngeal carcinoma (UCNT) is the most common subtype and regularly associated with Epstein-Barr virus (EBV). UCNT is sensitive to radiotherapy and to some chemotherapies. While early-stage tumours are most often treated with radiotherapy alone, recurrence is frequent in advanced disease. The aim of this study was to evaluate a neoadjuvant approach with chemotherapy (CT) and radiotherapy (RT).

Methods: This is a multinational multicentre non-randomised Phase II trial. Patients (pts) with previously untreated locally advanced UCNT (type II and III WHO), stage III, IVA and IVB, and lymph nodes >3 cm (UICC/AJCC 1997), received 3 cycles of a 3-weekly combination of docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2, followed by conventional standard RT 3–6 weeks later. Primary objectives were clinical response rate after CT and also after RT, evaluated according to RECIST criteria.

Results: Between July 2002 and May 2003, 66 pts (43 male/23 female) were included in 6 centres (1 in Tunisia, 1 in Algeria, 4 in Morocco). Median age was 48 (18–73), median performance status was 0. Thirty-one pts were stage III, 16 stage IVA and 19 stage IVB. 64 pts (97%) received the planned 3 cycles of CT, followed by RT in 59 pts. Response data are currently available for 49 pts after CT and 37 pts after RT. The overall response rate (RR) after neoadjuvant CT was 92% (18% complete responders [CR]/74% partial responders [PR]). There were 2% stable disease and 6% progressive disease (PD). A biopsy was performed on 39 pts, of whom 72% had complete sterilisation. Clinical RR after RT was 97% (83.5% CR/13.5% PR), and 3% PD (1 pt). Four pts died during the study: 3 due to PD (2 after Cycle 1 and 1 after RT), and 1 due to septic shock after the third cycle. Safety: most often seen grade 3/4 toxicities were alopecia (42%), vomiting (8%), stomatitis (6%).

Conclusions: This study demonstrated the high sensitivity of advanced UCNT to docetaxel–cisplatin followed by radiotherapy, with an acceptable safety profile.

*Data presented in the poster are updated from those reported in the abstract.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) comprises about 85% of all malignant lesions in the nasopharyngeal region. The incidence of NPC is high in some specific ethnic groups and geographical areas; an intermediate incidence of NPC is seen in North Africa, where undifferentiated carcinoma of nasopharyngeal type (UCNT) is the most common subtype. The aetiology of UCNT is multifactorial, and can involve viral (Epstein-Barr virus), genetic and environmental factors.[1]

UCNT is sensitive to radiotherapy and some chemotherapies. Although early-stage tumours are commonly treated with radiotherapy alone, disease recurrence is frequent when this approach is used in advanced disease. This has led to an interest in the use of neoadjuvant chemotherapy followed by radiotherapy in order to improve disease outcomes in advanced UCNT.

Cisplatin–5-fluorouracil (CF) represents the most commonly used induction chemotherapy in patients with squamous cell cancer of the head and neck (SCCHN); however, overall survival rates with this combination are disappointingly low.[2–3] Other combination regimens should be investigated to try to improve survival outcomes. Taxanes (docetaxel and paclitaxel) in combination with platinum agents have shown response rates of 23 to 53% in recurrent or metastatic SCCHN.[4–8] Furthermore, neoadjuvant therapy with docetaxel plus CF is superior to neoadjuvant CF alone before radiotherapy, in terms of response rate, overall survival and better tolerability, in patients with SCCHN.[9–11] This Phase II study evaluated the combination of docetaxel and cisplatin as neoadjuvant chemotherapy followed by radiotherapy in patients with locally advanced UCNT.

OBJECTIVES

Primary objective

- Response rate after chemotherapy and radiotherapy.

Secondary objectives

- Pathological response rate
- Duration of response
- Time to progression (TTP)
- Overall survival
- Safety profile.

METHODS

Key inclusion criteria

- Patients with previously untreated locally advanced UCNT (World Health Organization types II and III), TNM (International Union Against Cancer/American Joint Committee on Cancer [UICC/AJCC] classification 1997) stage III, IVA or IVB, lymph nodes >3 cm diameter and no distant metastases
- Age 20–75 years
- Adequate haematological, liver, renal and cardiac functions
- Written informed consent.

Study design and treatment

- In this ongoing multinational, nonrandomised Phase II trial, patients received 3 cycles of docetaxel 75 mg/m^2 in combination with cisplatin 75 mg/m^2 at 3-weekly intervals, followed by standard radiotherapy 3–6 weeks later.

Outcome measures and statistics

- The response rate was assessed (using the Response Evaluation Criteria In Solid Tumors [RECIST] by computed tomography [CT] scan) after the 3 cycles of chemotherapy, after the radiotherapy and every 12 months. At follow-up, clinical evaluations were performed every 3 months. CT scans were reviewed centrally by an independent radiologist.
- TTP and overall survival were evaluated using the Kaplan–Meier method.
- Safety was assessed using National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2).

RESULTS

Patient and tumour characteristics

- Between July 2002 and May 2003, 66 patients at 6 centres (4 in Morocco, 1 each in Tunisia and Algeria) were recruited onto the trial (intent to treat population [ITT]). Table 1 summarises the baseline patient characteristics.

CHARACTERISTIC	VALUE
No. of treated patients	**66**
Median age, years [range]	**44 [18–73]**
Sex, n (%)	
Male	**43 (65)**
Female	**23 (35)**
Karnofsky performance status, n (%)	
70%	**4 (6)**
80%	**9 (14)**
90%	**40 (61)**
100%	**13 (20)**
TNM stage, n (%)	
III	**31 (47)**
IVA	**16 (24)**
IVB	**19 (29)**
No. of lymph nodes involved, n (%)	
1	**4 (6)**
2	**43 (65)**
3	**19 (29)**
Histological type	
Non-keratinising	**2 (3)**
Undifferentiated carcinoma	**61 (92)**
Other	**3 (5)**

Table 1. Baseline demographics and disease characteristics (intent to treat population [n=66])

Treatment administered

- In total, 63 patients (95%) received the planned 3 cycles of docetaxel–cisplatin, of whom 59 patients (89%) subsequently received radiotherapy. Patients received a median of 7 (range: 1–10) weeks of radiotherapy, with a median total dosage of 65 (range: 3–72) Gy. Ten patients discontinued treatment (3 during chemotherapy, 4 after chemotherapy but before radiotherapy and 3 during radiotherapy) due to: withdrawn consent (n=2), lost to follow-up (n=2), death (n=3), disease progression (n=1) and other reasons (n=2).
- There was an unexpectedly high number of nonevaluable patients according to RECIST assessment (14 [21%] post chemotherapy, 23 [35%] post radiotherapy), mainly owing to technical problems (eg CT scans not done/lost/unclear).
- Overall, 6 patients (9%) had cycle delays due to: adverse events unrelated to treatment (n=3), consent withdrawal (n=2) and protocol deviation (n=1). No dose modifications were required.

Response

- The response rate (RECIST assessment) after chemotherapy was 68% (95% CI, 56–79%), the response rate after radiotherapy was 47% (95% CI, 35–60%) and the best overall response rate was 73% (95% CI, 60–83%). Table 2 shows details of the tumour responses.

	NO. OF PATIENTS (%)		
	AFTER CHEMOTHERAPY	AFTER RADIOTHERAPY	BEST OVERALL RESPONSE
Complete response	8 (12)	25 (38)	29 (44)
Partial response	37 (56)	6 (9)	19 (29)
Stable disease	1 (2)	0 (0)	0 (0)
Progressive disease	2 (3)	1 (2)	2 (3)
Nonevaluable	14 (21)	23 (35)	12 (18)
Missing	4 (6)	11 (17)	4 (6)

Table 2. Response rates (RECIST assessment) (intent to treat population [n=66])

- Table 3 shows the clinical response rates, which summarise the clinical response of lymph nodes by unidimensional measurement and were assessed because of the large number of patients that were nonevaluable using RECIST assessment. The overall clinical response rate was 86% after chemotherapy and 82% after radiotherapy.

	NO. OF PATIENTS (%)			
	AFTER CHEMOTHERAPY	AFTER RADIOTHERAPY	FOLLOW-UP 1[a]	FOLLOW-UP 2[b]
Complete response	34 (52)	47 (71)	47 (71)	25 (38)
Partial response	23 (35)	7 (11)	0 (0)	0 (0)
Complete response + Partial response	**57 (86)**	**54 (82)**	**47 (71)**	**25 (38)**
Stable disease	3 (5)	0 (0)	0 (0)	0 (0)
Progressive disease	2 (3)	1 (2)	1 (2)	2 (3)
Nonevaluable	0 (0)	2 (3)	0 (0)	0 (0)

[a]3 months. [b]6 months.

Table 3. Clinical response rates (intent to treat population [n=66])

- Pathological response rates (ITT population) were: complete disappearance of any lesion (28/66 [42%]); no modification of tumour aspect (11/66 [17%]); data missing, mostly due to difficulties in performing valid biopsy of the primary tumour site (27/66 [41%]).

Time to progression and survival

- Median TTP, response duration and overall survival have not yet been reached. The Kaplan–Meier curve for TTP to date is shown in Figure 1.

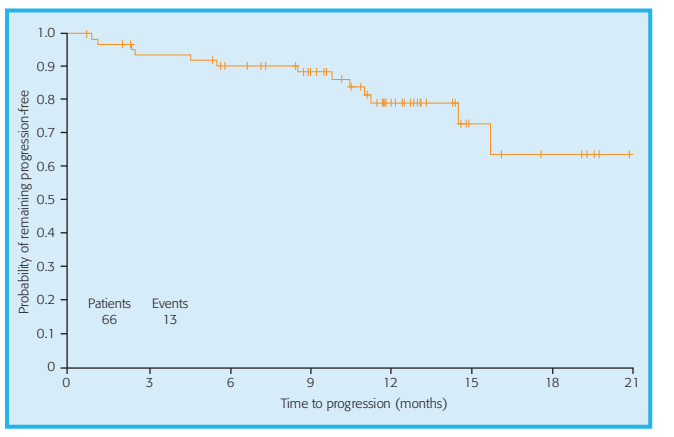

Figure 1. Time to progression (intent to treat population [n=66]).

- The Kaplan–Meier plot for overall survival rate is shown in Figure 2. Eleven patients had died as of July 2004: 4 during the study (3 due to progressive disease [2 after chemotherapy Cycle 1 and 1 after radiotherapy], and 1 because of septic shock after Cycle 3) and 7 in the subsequent follow-up period.

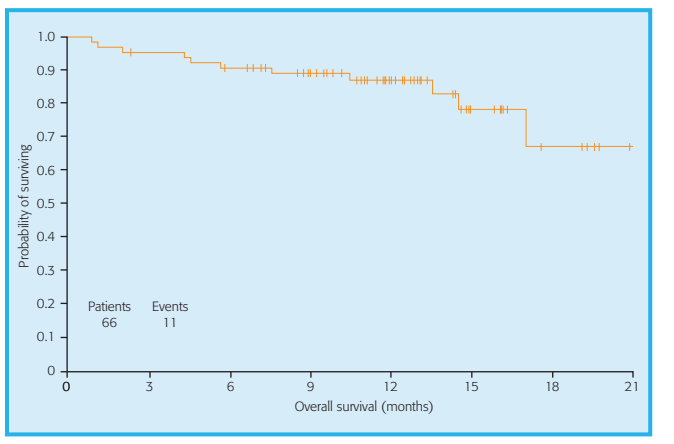

Figure 2. Overall survival (intent to treat population [n=66]).

Safety profile

- Docetaxel–cisplatin combination had an acceptable toxicity profile. The most common grade 3–4 nonhaematological adverse events reported in ≥5% of patients were stomatitis and vomiting (Table 4). Four patients had a serious adverse event: vomiting (n=2); febrile neutropenia (n=1); headache (n=1).

	NO. OF PATIENTS (%)	
	ALL REPORTED TOXICITIES	TOXICITIES CONSIDERED RELATED TO STUDY MEDICATIONS
Stomatitis	4 (6)	3 (5)
Vomiting	5 (8)	4 (6)
Febrile neutropenia	1 (2)	1 (2)

Table 4. Grade 3–4 nonhaematological toxicities occurring in ≥5% of patients plus haematological serious adverse events (safety population [n=66])

SUMMARY OF RESULTS

- The overall response rates (RECIST assessment) after neoadjuvant docetaxel–cisplatin chemotherapy and radiotherapy were 68% (8 complete responses [CR] and 37 partial responses [PR]) and 47% (25 CR and 6 PR), respectively, while the clinical response rates (based on clinical assessment of lymph node response) were 86% (34 CR and 23 PR) and 82% (47 CR and 7 PR), respectively.
- The chemotherapy combination had an acceptable toxicity profile. The most common grade 3–4 nonhaematological toxicities were stomatitis (6%) and vomiting (8%).

CONCLUSION

- **Locally advanced undifferentiated cancer of nasopharyngeal type is highly sensitive to neoadjuvant chemotherapy with docetaxel–cisplatin followed by radiotherapy. This therapy regimen has an acceptable toxicity profile.**

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References

1. World Health Organization (WHO). Approaches to cancer control. Available at http://www.who.int/cancer/media/en/411.pdf (accessed on 9 Sept 2004).
2. Domenge C, Hill C, Lefebvre JL, et al. Br J Cancer 2000;83:1594–1598.
3. Paccagnella A, Orlando A, Marchiori C, et al. J Natl Cancer Inst 1994;86:265–272.
4. Fountzilas G, Skarlos D, Athanassiades A, et al. Ann Oncol 1997;8:451–455.
5. Specht L, Larsen S, Hansen H. Ann Oncol 2000;11:845–849.
6. Pivot X, Cals L, Cupissol D, et al. Oncology 2001;60:66–71.
7. Glisson BS, Murphy BA, Frenette G, et al. J Clin Oncol 2002;20:1593–1599.
8. Baur M, Kienzer H-R, Schweiger J, et al. Cancer 2002;94:2953–2958.
9. Vermorken JB, Remenar E, Van Herpen C, et al. J Clin Oncol 2004;22(14 Suppl.):5508 [Abstract].
10. Johnson FM, Garden A, Kies M, et al. Proc Am Soc Clin Oncol 2003;22:510 [Abstract 2053].
11. Schwartz D, Yueh B, Montgomery RB, et al. Proc Am Soc Clin Oncol 2003;22:506 [Abstract 2038].