Eur J Cancer, Vol. 28A, No. 11, pp. 1792–1797, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Alternating Chemo-radiotherapy with Cisplatin and 5-Fluorouracil plus Bleomycin by Continuous Infusion for Locally Advanced Undifferentiated Carcinoma Nasopharyngeal Type

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More than 80% of undifferentiated carcinoma nasopharyngeal type patients with N3 disease (AJC-UICC 1987) will die with or from distant metastases within 3 years after the first symptom. From February 1986 to November 1987 30 consecutive patients with very advanced local disease were entered in a programme with chemotherapy–radiotherapy (CT–RT) alternation after a thorough work-up to eliminate the possibility of distant metastases. Protocol: two cycles of cisplatin 100 mg/m^2 day 1, bleomycin 15 mg intravenously day 1 and 16 mg/m^2 per day by continuous infusion days 1–5; 5-fluorouracil (5-FU) 650 mg/m^2 per day by continuous infusion days 1–5 4 weeks apart. This was followed by two series of high-energy radiotherapy, 35 Gy/3.5 weeks, with a third chemotherapy cycle in between. 27 men and 3 women were treated, the median age was 37 years (range 17–71) and the mean WHO performance status was 1 (range 0–3). TNM classification: 15 T4, 9 T3, 6 T2, 28 N3 and 2 N2c. 18 patients had nodes larger than 8 cm and 24 had bulky bilateral cervical nodes. Toxicity for this protocol was moderate, nausea and vomiting being the main side-effects. Results after two CT cycles were 3 complete responses (CR; 10%), 22 partial responses (PR; 73%), 2 disease stabilisations, 2 progressions, and 1 patient inevaluable. Of the 30 patients, 27 patients completed the CT–RT protocol, 2 patients died before radiotherapy and 1 refused treatment after 2 days on protocol. 25 patients were in CR 3 months after the end of radiotherapy. As of August 1991, with a median follow-up of 55 months (range 43–63), there are 17 patients alive, 2 of them with active disease and 15 are NED (2 after salvage therapy).
Eur J Cancer, Vol. 28A, No. 11, pp. 1792–1797, 1992.

INTRODUCTION

UNDIFFERENTIATED CARCINOMA nasopharyngeal type is a histologically characteristic and geographically prevalent cancer. The high incidence (18 per 100 000 per year) in Southern China and Southeast Asia makes undifferentiated carcinoma nasopharyngeal type one of the first causes of cancer death in these areas [1]. An intermediate level of incidence is reported in the Mediterranean basin (5–9 per 10^5 per year) [2], whereas in Japan, Europe and America undifferentiated carcinoma nasopharyngeal type is rare (0.1–0.5 per 10^5 per year).

Undifferentiated carcinoma of the nasopharyngeal type appears as a particular head and neck tumour of epidermoid lineage. One of its distinct characteristics is the highly frequent metastatic spread, correlated with bulky cervical nodes [3–6]. These systemic metastases, often clinically and radiologically silent for many months, are the main cause of therapeutic failure. It has a relatively short natural history with 80% of distant metastases discovered within 18 months of the first symptoms [7]. It is closely associated with the Epstein Barr virus (EBV), with a characteristically high EBV serology pattern [8, 9], and the presence of EBV genome in the tumoral cells is a constant finding [10].

The main survival prognostic factor in locoregional disease is bulky nodal invasion (N3 AJC-UICC) [11] associated with a high metastatic spread and a lethal prognosis (< 20% 5-year survival) [4, 7, 12, 13]. The advanced T stage (T4) with evidence of bony destruction and/or cranial nerve involvement is associated with a higher rate of local relapse or non-sterilisation [14]. When treated with appropriate sources, doses and techniques only 10–20% of patient deaths are due to isolated local recurrence or non-sterilisation.

Undifferentiated carcinoma nasopharyngeal type is traditionally treated with radiotherapy since the tumour is radiosensitive and radiocurable, and surgical resection unfeasible. Local control is obtained with adequate radiotherapy (RT) alone for bulky nodal disease patients in approximately 60–70% of patients but less than 20% 5-year survival is expected in this category [12–15].

Undifferentiated carcinoma nasopharyngeal type is also very chemosensitive [16, 17]. Systemic chemotherapy has been used in a variety of ways in an attempt to increase local control and survival: with neoadjuvant intent [18–21], adjuvant [22–26] and with concomitant radiation [15, 27, 28]. There is still great debate, however, regarding its place and contribution in increasing curability.

Alternating chemo-radiotherapy (CT–RT) schedules have proven their efficacy in other rapidly growing tumours such as

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Revised 18 Mar. 1992; accepted 1 Apr. 1992.

non-Hodgkin lymphoma [29] and small cell lung cancer [30] which, like undifferentiated carcinoma nasopharyngeal type, are both chemo- and radiosensitive. With the encouraging results of our PBF chemotherapy programme in recurrent and/or metastatic disease (79%) objective response with 20% of patients having complete response [31], we decided to treat the most locally advanced undifferentiated carcinoma nasopharyngeal type population with the CT–RT alternance after an intensive work-up to eliminate the possibility of detectable distant metastases. The deliberate choice of bulky nodal disease as the main eligibility clause was made to test the eventual role of chemotherapy in the population with the highest metastatic risk, as well as the lowest neck local control [7, 31–33].

PATIENTS AND METHODS

Between March 1986 and October 1987, 30 consecutive previously untreated patients with locally very advanced undifferentiated carcinoma nasopharyngeal type (N3 disease) were treated with an alternating CT–RT sequence.

All eligible patients had histologically proven undifferentiated carcinoma nasopharyngeal type, a negative metastatic work-up [7], and all had the undifferentiated carcinoma nasopharyngeal type characteristic anti-EBV serology consisting of an elevation of the immunoglobulins IgG and IgA antiviral capsid antigen (VCA) and early antigen (EA). When there were doubts concerning the histology, immunohistochemistry studies were performed to eliminate non-Hodgkin lymphoma (leukocyte common antigen) or differentiated squamous cell carcinoma [KL1 (keratine 6)].

Pretreatment work-up and staging procedures included: history and physical examination, height, weight and body surface area, ENT examination under general anaesthesia with biopsy, laboratory exams including complete blood count (CBC), erythrocyte sedimentation rate (ESR), 24-h urine creatinine clearance, complete biochemical profile (SMA_{12}), lactic dehydrogenase, EBV serology (IgG and IgA antiVCA and EA), bone marrow biopsy, chest X-ray, computerised tomography (CT) of the head and neck, bone scintigraphy, abdominal echography or CT.

Clinical staging was determined according to the AJCC-UICC 1986 TNM system [11].

The protocol consisted of two cycles of neoadjuvant chemotherapy given 4 weeks apart. The third cycle was intercalated between two series of 3½-week double-split course radiation therapy.

The chemotherapeutic regimen, also used in our first metastatic and/or recurrent NPC series [31], consisted of: cisplatin 100 mg/m² intravenously day 1; bleomycin 15 mg intravenously push day 1, then 5 days continuous infusion of both bleomycin 16 mg/m² per day and 5-FU 650 mg/m² per day. Adequate renal, marrow and liver functions were required before each cycle, functional respiratory tests with DCLO were performed after two cycles of chemotherapy.

Radiotherapy was delivered by ^{60}Co or 4 MEV linear accelerator at a daily dose of 2 Gy, five fractions per week as two sequences of 35 Gy, sandwiching a third cycle of PBF chemotherapy and separated by a gap of 2–3 weeks. The total dose is 70 Gy in 7 weeks to the nasopharyngeal tumour and its extension, 65 Gy in 6.5 weeks to the involved node areas and 50 Gy in 5 weeks to the rest of the neck. After the nasopharyngeal and upper cervical nodes had received 42 Gy, the two lateral opposed fields were reduced to exclude the spinal cord. The posterior neck lymph nodes were then boosted with 8 Gy (prophylactic) to 28 Gy (clinically involved nodes) with 3–9 MEV electrons through small lateral fields. The lower neck and subclavicular fossa were treated with a single anterior field to 50 Gy in 5 weeks with the larynx and spinal cord shielded. Palpable nodes were boosted up to a total dose of 65 Gy.

Table 1. Patient characteristics (TNM)

	T2	T3	T4	Total
N2c	0	1	1	2
N3	6	8	14	28
Total	6	9	15	30

Toxicity was evaluated according to WHO criteria except for late toxicity which was evaluated according to RTOG late effects scoring criteria [34]. The response evaluation according to the WHO criteria is done by the same oncologists 2 weeks after the second cycle of chemotherapy, with clinical examination, fibroscopy and CAT scan imaging. Biopsy of suspicious area was done at the end of radiation therapy. The evaluation was repeated 3 months after the entire protocol, and then every 6 months. This evaluation included the same systemic work-up done initially except for the bone marrow biopsy, used only to confirm positive bone scans. The survival rate was calculated from the first day of initial chemotherapy until death or last follow-up contact. Time to progression was calculated from the first day of treatment until first evidence of disease progression. Survival and time to progression were estimated as described by Kaplan and Meier [35].

RESULTS

Patient characteristics

There were 27 men and 3 women, from different ethnic origins: 23 North Africans, 4 Italians, 2 Black Africans and 1 French. Median age was 37 (range 17–71). Most of the patients had a performance status (WHO) of 0 (43%) or 1 (30%). The distribution of patients according to T and N is shown in Tables 1 and 2. Overall, 50% of patients had evidence of bone destruction and/or cranial nerve involvement (T4), 28 patients had very advanced nodal disease (N3) larger than 8 cm in 18 of them and 24 patients had bulky bilateral cervical nodes. Trismus due to tumoral invasion was seen in 2 patients. Paraneoplastic syndromes [7] were seen in 7 patients including: 2 tumour-specific fevers, 4 leukemoid reactions (defined as leucocytes over 20 000 and platelets over 450 000), and 1 osteoarthropathy.

Toxicity

Toxicity (Table 3) after 89 cycles consisted mainly of nausea and vomiting despite high dose of antiemetics, moderate mucositis becoming grade III (RTOG) at the end of radiotherapy in all patients. Alopecia was constant and reversible. Haematologic

Table 2. Tumour extension as defined by CT

Skull base erosion	15
Extension to the oropharynx	7
Extension to the nasal cavities	3
Extension to the maxillary sinus	3
Intracranial involvement	3
Cranial nerve involvement	7

(The same patient may have multiple extensions).

Table 3. Acute and late toxicity (WHO-RTOG)

Acute (WHO): 89 cycles evaluable	
Nausea–vomiting	Grade II: 16 cycles
	Grade III: 61 cycles
Neutropenia	Grade II: 1 cycle
Alopecia	Grade III: all patients
Mucositis (RTOG)	
Post CT_2	Grade II: 12 patients
	Grade III: 2
	Grade IV: 1
End of RT	Grade II: 9 patients
	Grade III: 13
	Grade IV: 5
Reversible weight loss (5–10%) at the end of RT: 50% patients	
Late toxicity (RTOG)	
Xerostomia	All patients
Trismus	3 patients
Fibrosis of cervical tissues	3 patients
Velar atropy	3 patients
Cranial nerve palsy	2 patients
Radiation myelitis	1 patient

tolerance was excellent with only one grade II toxicity episode. There were no delays for the entire 30 patient series, and the compliance was excellent (97%). 5–10% reversible weight loss was common (50% of patients) but without general status deterioration. No renal or pulmonary toxicity episodes were seen. The chemotherapy-induced toxicity was mild, as hoped for in neoadjuvant chemotherapy protocol design. Late effects are as shown on Table 3, mainly consisting of xerostomia and trismus. 1 patient developed a syndrome compatible with radiation myelitis.

Response to treatment

Of the 30 patients entered in this protocol, one did not complete the first chemotherapy cycle, and refused further treatment. Since the aim of this trial was to do a phase II on all consecutive eligible patients, and report on final results, percentages have been calculated including all patients entered. 3 patients had a complete response to chemotherapy (10%), with histological confirmation in 1 patient. 21 patients (73%) had a partial response, in all cases amply exceeding the 50% reduction standard in the product of diameters. 2 patients had disease stabilisation and 2 patients had progressive disease, with the first-mentioned patient being inevaluable.

Of the 29 patients completing the first two cycles of chemotherapy, 1 died of an unrelated cause after a partial response (acute lower aortic obstruction from atherosclerotic disease), and 1 of the progressive-disease patients had a 10% Karnofsky performance status motivating therapeutic abstention. Therefore, only 27 patients had the radiotherapy/chemotherapy alternance plan with a full dose of radiation therapy. 3 months after the end of radiotherapy, 25 patients were in complete response (83% of the series). 1 patient, a minor responder to initial chemotherapy, developed liver metastatic disease while completing radiotherapy, and 1 patient with massive base of the skull (T4) erosion did not achieve local control. Thus, 25/30 patients entered (83%) achieved a complete response and local control after the entire therapeutic sequence.

As of August 1991, and with a median follow-up of 55 months (range 43–63) there are 15 patients alive, 2 of them with active disease. Of the 13 patients currently NED (43+–61+) 11 are continuously in first remission, and 2 are free of disease 18 and 23 months after salvage therapy (CT+RT) for single metastatic lesions diagnosed 35 and 12 months after the initial treatment. The actuarial overall survival in August 1991, with a minimum 43 months follow-up and a median of 55 months, (Kaplan–Meier) stands at 52% (Fig. 1).

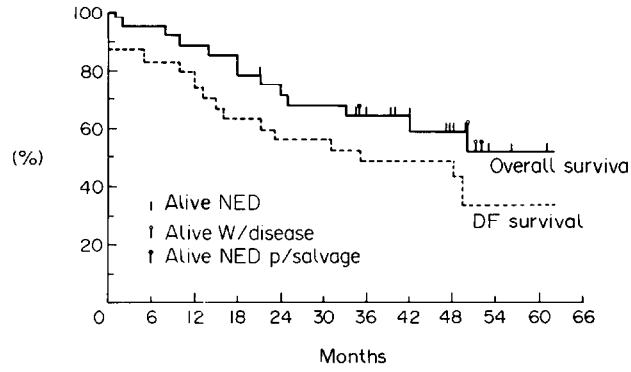

Fig. 1.

Failure after treatment completion on the 29 evaluable patients shows: 1 non-sterilisation (T4) who also developed bone metastasis at 10 months; 1 patient developed a cervical cord compression syndrome probably by direct erosion of a local recurrence but the possibility of myelitis was not excluded; 1 patient developed a late (31 months) paraspinal/retropharyngeal recurrence at the RT field border; 3 patients developed single metastatic disease lesions 12, 16 and 35 months after treatment, all of them successfully salvaged with CT–RT, albeit 1 of those 3 who recovered from a paraplegic episode after epidural disease redisseminated after a new disease-free period of 24 months. The other 11 patients had disseminated metastatic disease as the cause of failure. All metastatic patients except 3 had their relapse within 2 years of treatment completion. As of 1 August 1991, 11 patients died (2 are presumed dead after being lost to follow-up: 1 in progression after refusal, 1 of radiation-induced myelitis) and 1 patient was in complete response before we lost contact at 21 months. The other deaths are as explained above (Leriche syndrome in 1 patient, and progressive metastatic disease in all the rest). The disease-free survival actuarial plot can also be seen in Fig. 1, with 13 patients continuously disease-free, establishing a 35% disease-free survival rate after 43 months minimum follow-up.

DISCUSSION

Nasopharyngeal carcinoma has been traditionally treated with radiotherapy alone. Although the probability of cure for patients with stages I and II AJCC is high [15, 36, 37] ranging between 72 and 96%, the probability of cure for patients with advanced stage (III and IV) disease is poor because of the higher rate of locoregional and distant failure, especially in the undifferentiated type. Distant failure is linked to the presence of bulky nodal disease, and in undifferentiated carcinoma nasopharyngeal type it seems to be far more frequent than in the SCC variety.

Despite technical improvements introduced in recent years (use of higher dosages, larger fields and fractionation modifications [38–40]), the results of RT remain without major changes, with overall 5-year survival rates ranging between 20 and 60%. In the N3 subgroup, the prognosis is worse with 5-

Table 4. Literature review of RT results in the treatment of advanced undifferentiated carcinoma nasopharyngeal type

Authors (No. of patients)	N3*	UCNT	Radiation technique	5-year survival
Mesic 1981 MD Anderson (251)	50% AJC (1977)	45%	Continuous	52%
Hoppe 1976 Stanford (78)	22% UICC (1962)	36%	Continuous	59%
Dexing 1988 China (1379)	III-30% IV-47% Chinese	34%	Continuous	Stage III—30% Stage IV—29.2%
Pontvert 1987 Paris (139)	72% UICC (1978)	74%	Continuous	30%
A. Chu 1984 Philadelphia (80)	31% AJC (1977)	24%	Continuous	27% (N3)
Huang 1980 Taiwan (1306)	48% HO Class	87.5%	Continuous 70 Gy every 7 weeks	29.1% (N3)
Frezza 1986 Bologna (986) (41)	36% UICC (1978)	56%	Continuous	35% (N3)
Schwaab 1983 Villejuif (143)	48%	72%	Continuous	30% (N3)
Wang 1989	30%		Accelerated	85% (Two times per day)
Boston (60)	UICC (1986)	?	Hyperfraction	53% (Once a day not randomised)
Ho 1981	IV 22%			
Hong Kong (1654)	HO Class	> 95%	Hypofraction	21.9%

year survival often below 15% [12–14, 41, 43] and only a small number of such patients are cured.

Table 4 shows the 5-year survival after definitive radiation therapy in relation to the extent of disease, histology and the radiation technique used. Initial results with conventional fractionation [32, 37, 41–46] are still poor and have motivated clinical trials with altered fractionation schemes.

Hypofractionation as described and advocated by Ho *et al.* [12] is associated with an unacceptably high frequency of complications and severe late sequelae [12].

Hyperfractionation and accelerated hyperfractionation (A.H.) schedules [38–40] have suggested therapeutic gains, but a recent report from Hong Kong [47] found no benefit in the use of A.H. vs. continuous RT in a randomised controlled trial in undifferentiated carcinoma nasopharyngeal type.

The use of split course radiation is associated with less late toxicity and better tolerance, particularly when high dose radiation is used [33].

All these attempts failed to demonstrate a substantial benefit to survival because of the frequent metastatic spread clinically evident after radiation therapy. This points to the need for effective adjunctive systemic chemotherapy to erradicate microscopic disease.

Furthermore, most of the series published within recent years have different staging systems (Ho, AJCC, UICC, RTOG, Chinese and AJCC-UICC). In all of them, only a summary pretherapeutic work-up is done in the absence of symptoms. These reports consist of retrospective analysis of NPC patients treated with different techniques and doses (continuous, split course, hypo- and hyperfractionation) and they contain mixed histology populations (squamous cell carcinoma and undifferentiated carcinoma nasopharyngeal type) in variable proportions in the non-Asiatic series.

The present study is of particular value since it is the first one to incorporate prospectively all consecutive patients with bulky nodal disease to a phase II trial of CT–RT, after a complete work-up to eliminate patients with metastatic disease.

The high degree of local control in the present series is remarkable, given the homogeneous nature of high tumoral volume patients, both at T and N (Tables 2 and 3). Only three failures at T or N have been seen (89% local disease control) with a minimum 4-year follow-up. This points to a regional cooperation between radiotherapy and chemotherapy. Other authors have observed a better control in local disease in other neoadjuvant or concomitant CT–RT head and neck SCC trials [20, 48].

The many other reports published with chemotherapy before, with or after radiotherapy are informative and optimistic, but easily criticised because of their retrospective nature or their comparison with historical controls. We will try to analyse and comment on the more relevant ones.

A review of the literature on the chemotherapy experience in locoregional and metastatic nasopharyngeal cancer shows that the known active chemotherapeutic agents include cisplatin, cyclophosphamide, doxorubicin, 5-fluorouracil (5-FU), bleomycin and methotrexate. Several regimens have been used and reported as phase II trials.

The postradiotherapeutic adjuvant chemotherapy series [22–26] has always found therapeutic benefit based on retrospective studies with historical controls. Although some benefit may exist with this approach, there has been failure to show any effect in controlled trials. The bias of patient selection is very strong since only patients free of metastatic disease for at least 4 months from diagnosis are eligible. Neoadjuvant chemotherapy has been suggested as a means of improving both local control and long-term survival when compared with historical radiation therapy series [15, 19]. Huang reported 64% 5-year survival for his N2 category (bilateral > 5 cm) patients receiving chemotherapy with different combinations and sequences including cisplatin–bleomycin, cyclophosphamide and methotrexate, and only 49% for those treated with RT alone [15].

At Detroit, an overall response of 75% and a CR of 50% were achieved with cisplatin–5-FU induction chemotherapy [20]. Dimery [18] has also used this approach and found improved local control, survival time and disease-free survival when compared with his historical series treated by radiation therapy alone. Several other authors reported similar results with the use of initial chemotherapy [21, 48, 49]. The American experience at M.D. Anderson with cisplatin–5-FU postRT, and the Wayne State with both simultaneous cisplatin/RT [27] are being used together as the test treatment arm which is already being prospectively tested on an Intergroup trial basis against standard RT [50].

The recently published RTOG experience [27] emphasising the usefulness of simultaneous cisplatin and radiotherapy may be right in its conclusion, but the data are poor. It consists of a subgroup analysis of a larger RTOG trial, with 27 patients collected over 8 years on a multicentric basis. Median follow-up is only 17 months (1+–95+), without histologic or serologic patient definition, without specification of nodal disease status and with more than one third of patients not completing the planned treatment. Their results are not analysed by failure pattern.

Two reports have made the role of CT questionable. The first from Milan [23] is a randomised adjuvant trial with an inadequate low-dose intensity non-cisplatin-containing regimen and 10% of patients refusing chemotherapy in the CT–RT arm. The second, from the Princess Margaret Hospital [19], is a comparison between historical RT and a retrospective CT–RT series.

We do not know of any other published series to date in NPC with a similar high tumoral volume homogenous population, and the level of local control rate of the present study. The role of cisplatin, bleomycin and fluorouracil in obtaining an effect should not be minimised. All three drugs have proven enhancing therapeutic effects when added to radiotherapy.

Our series is prospective, consecutive and homogeneous, and the only one including exclusively the most advanced locoregional disease patients (93% of N3 and 50% of T4). It shows 10% CR and 83% overall response to initial chemotherapy and 92.5% local control after completion of the entire protocol. The 4-year estimated survival is 52%, with 30% of patients alive NED at over 46 months.

The midterm results in disease-free survival are also well above reported experiences, with a 35% continuous NED rate that seems solid enough with a 4-year minimum follow-up.

Although our compulsive work-up has never been done before in such patients, and all the entered patients had no clinical evidence of metastatic disease before starting chemotherapy, there have been at least 14 metastatic patients after chemotherapy, most within 2 years of treatment. We did not expect a great preventive effect on disseminated microscopically metastatic patients, since the CR rate to chemotherapy was only 10%. Furthermore, the role of the work-up itself as the origin of Will Rogers phenomenon [51] could be the determinant for our good results. We saw at least 30–40% of subclinical metastatic disease in N3 patients undergoing pretherapeutic work-up before this trial and the one that followed [7, 31, 52]. It is highly possible that much of the radiotherapy literature up until now is hampered by the bias of radiating patients already metastatic subclinically. Even if the local control and the disease-free survival compare favourably with any other published series, we feel that 14/27 patients metastasising is still too high a proportion to use the present protocol and schema as the test arm of a neoadjuvant trial in NPC.

This fact led us to intensify and optimise the present chemotherapy combination in order to promote an eventual systemic role of the neoadjuvant chemotherapy in the combined modality programme. Our current programme aims to test the usefulness of three cycles of neoadjuvant chemotherapy consisting of replacement of 5-FU by an anthracycline (Epirubicin), bleomycin and cisplatin given every 3 weeks: followed by 70 Gy in 7 weeks of continuous radiation therapy compared in a prospective multicentric randomised trial with RT alone. This association, which includes epirubicin, particularly adapted to subsequent radiotherapy given, its high tissue clearance rate, is probably the most active regimen in undifferentiated carcinoma nasopharyngeal type to date. Our pilot results [53] with this new approach have already been reported, and constitute the basis for a multicentric international randomised trial already in course.

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