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Results of Chemotherapy Plus External Reirradiation in the Treatment of Locally Advanced Recurrences of Nasopharyngeal Carcinoma

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Between 1982 and 1991, 16 patients with recurrent cancer of the nasopharynx were treated with chemotherapy (CT) and radiotherapy (RT). All patients had received prior RT (45–69, 30 Gy). According to rTNM there were three rT2, one rT3 and 12 rT4. 5 patients were N1. Reirradiation (12–46 Gy, mean: 28) started 3–4 weeks after CT (2–6 cycles of different combinations), but 2 cases involved concomitant therapy. Out of 16 patients 7 had complete response (CR) (43.7%), 7 partial response and 2 no response. Statistically significant prognostic factors for obtaining CR were time of relapse and response to initial CT. Median duration of CR was 22+ months (9–64+). Failures at primary site occurred in 3 patients, 2/2 of those receiving CT without platinum compounds and 1/5 of other ones, with statistically significant difference in local recurrence free-survival between the two groups. Two- and 3-year actuarial overall survival were 28% and 10%. Rates of disease-free survival were 17% and 8%, respectively. The acute toxicity was generally mild. No central nervous system damage or radiation-induced myelitis were observed in survivors.
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INTRODUCTION

FAILURE AT the primary site after curative irradiation in patients affected with carcinoma of the nasopharynx occurs in 10–60% of cases, according to T-stage [1]. In early stage recurrences, limited to the cavum, reirradiation could obtain high rates of long-term local control and survival; worse results, often with severe complications, have been reported in patients with more advanced lesions, extended beyond the nasopharynx and/or involving the base of the skull [2–7]. Systemic chemotherapy has been used in relapsing or disseminated nasopharyngeal lesions [8–14]; in spite of a comparatively good response rate, the duration of the remission was generally poor and the majority of patients had a progression within a few months. In different locally advanced or recurrent head and neck tumours, including nasopharynx, improvements have been reported in response rate and local control combining irradiation and chemotherapy [15–18]. This approach was also followed at the Radiation Therapy Department of the University of Turin in the retreatment of local recurrences of nasopharyngeal cancer. The medical records of patients who underwent the combined treatment were retrospectively analysed. They represent the basis of this report, in which we assess our experience in order to optimise further clinical protocols. The final evaluation was made on 30 November 1991.

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PATIENTS AND METHODS

Patients were not accepted if they had previous chemotherapy or evidence of distant metastases. Adequate renal, hepatic and bone marrow functions (white blood cells $\geq 3000/\mu l$, platelets $\geq 120\,000/\mu l$) were also required. Over a 9-year period, between March 1982 and April 1991, 16 patients, with pathological confirmation of recurrence, entered and were considered suitable for this analysis. All of them had received prior radiotherapy by ^{60}Co (9 of them at our own institution). The development of recurrence occurred within 30 months in 11 patients (68.7%); the others had their recurrences revealed after 32, 38, 81, 96 and 101 months, respectively. 7 patients (43.7%) complained of neurological symptoms due to cranial nerve involvement. 5 patients (31.2%) simultaneously developed neck nodes. In total, there were 4 patients at stage rIII and 12 (75%) at stage rIV. Other main characteristics of the patients are summarised in Table 1.

Treatment modality

In early years (from 1982 to 1985) we mainly used combination chemotherapy without platinum: VBM (vincristine, 1 mg/m^2, day 1, bleomycin, 15 U/m^2, day 1, 2, and methotrexate 200 mg/m^2, day 2) or VCA (vincristine, 1.2 mg/m^2, day 1, cyclophosphamide, 200 mg/m^2, days 1–4, and doxarubicin 40 mg/m^2, day 1); from the end of 1985, we elected to use different regimens, containing platinum compounds: COB (cisplatinum 100 mg/m^2, day 1, vincristine 1 mg/tot, day 2,5,

and bleomycin 30 U/tot, days 2–5) or cisplatinum/5-FU (cisplatinum 100 mg/m^2, day 1, 5-fluorouracil 1 g/m^2, days 1–5). Each cycle was repeated every 4 weeks, up to a maximum of 6 (total number of cycles: 58; mean: 3,6). In 2 cases chemotherapy (CBDCA/BLEO): carboplatin 100 mg/m^2, day 1, bleomycin 15 U/m^2, day 1) was administered weekly, concomitantly to irradiation.

Radiation therapy was generally scheduled to commence 3–4 weeks after the end of chemotherapy. Treatment was delivered by external megavolt units (^{60}Co photons, 6 MV or 18 MV X-rays) and consisted of three-fields (anterior, right and left posterior oblique) or arc rotation techniques. Total tumour dose, administered using conventional fractionation (1,8–2 Gy/fraction/day, 5 days a week), was comprised between 12 and 46 Gy (mean: 28.3 Gy). It was planned holding previous given dose and volume in the due consideration: in no case the addition of initial treatment and reirradiation exceeded the dose of 100 Gy. Positive neck nodes received 6–13 MeV electron beams up to a total dose of 35–48 Gy.

RESULTS

Response

Assessment of tumour response was performed by nasopharyngoscopy and computed tomography (CT) scan. On the whole series of patients, the overall response rate was 87.5%, with 7 complete response (CR rate: 43.7%). The median duration of CR was equal to 22+ months (range: 9–64+). Out of 14 patients in which drugs preceded irradiation, one had a complete response (CR) and 5 had a partial response (PR) after the initial chemotherapy. At the completion of the combined treatment the total number of responses increased to 12/14 (85.7%), with 5 CR (35.7%) and 7 PR. The other 2 patients who received concomitant radiochemotherapy had both CR. Major prognostic factors for obtaining CR were time of relapse (CR rate of patients with an interval of more than 30 months: 80%, of the other ones: 27.3%; $P<0.05$, Pearson χ^2 test; $P=0.07$, Fisher's exact test) and response to initial chemotherapy (responders: 66.7%, non-responders: 14.3%; $P<0.05$, Pearson χ^2 test; $P=0.06$, Fisher's exact test). Other variables influencing CR rate, however without statistically significant difference, were types of combination chemotherapy (including platinum compounds or not: $P=0.15$) and total dose of irradiation (less or over 30 Gy: $P=0.28$).

Survival

Two- and 3-year overall actuarial survivals were 28% and 10%, respectively. A statistically significant difference was found in the probability of survival between CR patients and the others (at 2 years 64% vs. 0%; $P<0.001$, logrank test).

Table 1. Patients' characteristics

Evaluable patients	16
Median age, years (range)	51 (37–67)
Sex (male/female)	9/7
Performance status ECOG 1, 2, 3	9, 6, 1
T-Stage, primary tumour	1 T1, 4 T2, 3 T3, 8 T4
Prior radiotherapy mean dose (range)	61,20 Gy (45–69,3)
Mean time for appearance of recurrences	32 months
Histology (undifferentiated, squamous)	14/2
rT-Stage, recurrent tumour	3 rT2, 1 rT3, 12 rT4
Site of recurrence (cavum/extracavum)	3/13

There also was a statistical trend ($P=0.07$) for better probability of survival of patients who had their relapses at least 30 months after initial radiotherapy compared with patients who had a shorter interval (at 2 years 75% vs. 12%). Two- and 3-year overall survivals were respectively of 50% and 24% in patients receiving platinum-based chemotherapy; in patients treated with VBM or VCA cycles there were no survivors after 3 years (13% after 2-years). This difference was not statistically significant ($P=0.22$). Local failures (cavum) occurred in 3 patients, 2/2 patients with CR after chemotherapy not including platinum compounds and 1/5 of other ones. A statistically significant difference was found in the probability of local recurrence free-survival between the two groups of patients (at 2 years 32% vs. 13%; $P<0.05$). 2 patients had neck recurrence after 6 and 9 months, respectively, with no signs of disease inside the cavum. Two- and 3-year rates of disease-free survival were 17% and 8%, respectively.

Acute and late toxicity

The acute toxicity of the combined treatment was generally mild. Haematological toxicity, mainly grade II/III leukopenia, occurred in 4 patients; a treatment delay was required for 2 of them. Radiation-induced mucositis (mostly grade II) occurred in almost all patients. With regards to late radiation effects, no central nervous system damage or radiation-induced myelitis were observed in survivors. Necrosis of the soft tissues inside the cavum was observed in 2 patients who complained of persistent rhinorrhoea.

DISCUSSION

Long-term survival for patients with recurrent head and neck cancer is generally poor, despite the ability of different therapies to reduce the tumour burden [19]. Nasopharyngeal carcinoma may represent the exception: good results have been reported, especially in early stage recurrences, using external reirradiation [2–4, 6, 7] or brachytherapy techniques [5]. All authors agreed that reirradiation requires high tumour dosages (60 Gy or more); however, the benefit of high boost dose is more apparent in early stage lesions [6, 20]. When these dosages are administered, high rates of treatment morbidity must be expected. Yan *et al.* [7], presenting their results of retreatment on 219 patients, reported 12% of radiation myelitis, 8% of radiation encephalopathy, 7% of cranial nerve palsy and 7% of soft tissue and osteonecrosis.

Good rates of response have been reported in relapsing or disseminated nasopharyngeal cancers using chemotherapy: the most active combinations included cisplatinum [8, 10–12, 14]. Unfortunately, most of these responses had an average duration of a few months, with a limited impact in improving survival. Several studies have documented a higher rate of reduction in tumour size combining active drugs and radiation therapy [15–17, 21, 18].

In the treatment of locally advanced recurrent cancer of the nasopharynx, we used the combination of chemotherapeutic agent(s) and low/moderate doses of reirradiation in order to (a) improve rate and duration of response to drugs by the addition of radiotherapy, and (b) reduce severe effects due to administration of higher dose of irradiation (60 Gy or more), as requested when this last one is employed alone. These objectives have been partially reached, as suggested by the results. After induction chemotherapy an overall response rate

of 42.8% was obtained; subsequent irradiation doubled this value (85.7%). On the whole series of patients submitted to the combined treatment, the CR rate (43.7%; median duration: 22+ months) was high, especially when compared to those obtained in patients with recurrent or metastatic UCNT at our own (15.6%) and other institutions [8, 10–12, 14]. This difference is significative, even if it is necessary to consider the favourable selection of patients in our actual series (none of them had distant spread of disease). On the whole series, the actuarial overall survival was 28% after 2 years and 10% after 3 years: these values are similar to those reported by Wang [6] in stage rT3 and rT4. Two- and 3-year disease free survival were 17% and 8%, respectively: Yan *et al.* [7] reported a rate of 14% after 5 years, in a series including earlier stages. Within bounds of the small number of patients forming our series and the relatively short period of observation, these results have been obtained with a minimal incidence of severe complications. In particular, no central nervous system damage or myelitis were observed in the few long-term surviving patients.

In summary, the combination of active chemotherapy and low/moderate dose of radiotherapy can be proposed in the management of recurrent carcinoma of the nasopharynx as a valid alternative to high dose reirradiation alone. The combination chemotherapy had to include platinum compounds. Response to initial chemotherapy is one of the most important prognostic factors and could allow to select patients for subsequent more aggressive therapy; in these cases we propose to administer a reirradiation dose of 40 Gy and add three course of adjuvant chemotherapy. High rate of failures in the neck suggests undergoing CR patients to prophylactic surgical neck dissection after the completion of the combined treatment.

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