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Combined therapy of undifferentiated carcinoma of nasopharyngeal type

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From November 1989 to October 1993, 339 patients with stage IV undifferentiated carcinoma of nasopharyngeal type (UCNT) were enrolled in a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin - BEC) plus radiotherapy (171 patients) vs. radiotherapy alone (168 patients). All patient characteristics were well-balanced in both arms. The overall response rate assessed clinically by the investigator at the end of chemotherapy was 91% (WHO) with 47% CR and 44% PR. Three months after the completion of radiotherapy, a CR (clinical + CT scan) was observed in 55% of the combined treatment group, compared to 34% in the radiotherapy-alone group ($p<0.01$). Tumor recurrence or progression was observed in 55/171 patients in the chemotherapy arm (32.7%), compared to 92/168 patients in the radiotherapy-alone arm (54.7%) ($p<0.01$). In conclusion, the addition of BEC type chemotherapy, preceding radiotherapy, has changed the proportion of UCNT patients continuously disease free but the overall survival data are not yet mature.

Key words: nasopharyngeal neoplasms-drug therapy-radiotherapy; treatment outcome

Introduction

As high as 85% of all nasopharyngeal tumors are carcinomas. The incidence of undifferentiated and poorly differentiated tumors is the highest, especially in endemic regions (over 90%). Undifferentiated carcinoma of the nasopharynx is an Epstein-Barr virus-related carcinoma of epidermoid origin different in its carcinogenesis, epidemiology and behaviour patterns from other squamous cell carcinomas of the head and neck.[1,2,3]

Carcinoma of the nasopharynx is a relatively rare tumor. In the United States and Western Europe, it accounts for only 0.2-0.3% of all malignant tumors,[4] or 1-3% of all carcinomas of the upper respiratory and digestive tract.[5] Its incidence is much higher in the Mediterranean countries (5-7 newly detected cases per 100,000 inhabitants a year).[6,7,8] In Southeast Asia, this number reaches 15-30 cases per 100,000 inhabitants and accounts for even 60-75% of upper respiratory and digestive tract carcinomas, or 20% of all malignant tumors.[9,10] Of all head and neck tumors, nasopharyngeal carcinomas are the fastest to metastasize.

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Treatment

Nowadays, radical surgery of nasopharyngeal carcinoma, has been almost completely abandoned. Treatment of nasopharyngeal carcinoma is primarily the concern of radiotherapy. The radiotherapy response in early-stage disease is usually successful, but the response of locally advanced disease is relatively poor, with local nodal failure reported in up to 40% of cases.[11-14]

Nasopharyngeal carcinoma, in particular that of poorly differentiated cells, is a chemosensitive tumor in which anticancer drugs figure prominently for years.[15-18] Formerly, chemotherapy was applied only in disseminated disease, while in the last ten years it is applied in early locally advanced cases.

Chemotherapy is sometimes applied alone or combined with radiotherapy as part of a multimodal therapy approach.

Results of numerous nonrandomized clinical trials have confirmed the advantage of polychemotherapy, and with the combination of cytostatic agents bleomycin, cyclophosphamid, methotrexate, and fluorouracil (BCMF) the therapy response is reported in 50-80% of patients.[19-29] Clinical trials on the efficiency of cisplatin (CDDP) based polychemotherapeutic protocols show the best results (86%).[30-34] Despite the well-known chemosensitivity of nasopharyngeal carcinoma, randomized prospective clinical trials on chemotherapy efficiency in metastatic disease have started only recently. In 1991, a clinical trial aiming at comparing the antitumor efficiency of cisplatin, bleomycin and fluorouracil (PBF) combination with the combination in which fluorouracil is replaced with epirubicin (BEP) was carried out at the Institute Gustave Roussy. The response rate assessed in both groups was 80%, but complete remission was observed only in 20% of patients of the first group and 13% of patients of the second group.[16]

Despite such promising results, no randomized trial testing the value of the added neoadjuvant chemotherapy has yet been reported, and it remains to be shown in a randomized trial whether the addition of neoadjuvant chemotherapy to conventional radiotherapy could improve the treatment outcome.

Phase II trial of bleomycin-epirubicin-CDDP regimen (BEC) in N2c-N3 patients showed a 98% objective response rate, including a high proportion of complete clinical responses (66%).[35] This high complete response rate contrasted with the lower complete response rate (10%) obtained in a comparable group of patients from the same institution related with CDDP-bleomycin-5FU,[15] suggests that BEC fulfilled the activity required for a prospectively controlled trial testing the value neoadjuvant chemotherapy in this type of tumor. With that aim, a large-scale randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV undifferentiated nasopharyngeal carcinoma was initiated in 1989, by the International Nasopharynx Cancer Study Group with the participation of Algeria, Croatia, Greece, France, Malaysia, Morocco, Portugal, Saudi Arabia, Spain and Turkey.

Material and methods

From November 1989 to October 1993, 339 patients were enrolled in this study. The eligibility criteria were as follows: biopsy-proven UCNT (World Health Organization type 2-3), age between 15-70, any T, N $\geq$ 2, M0 (UICC 1987), performance status 0-2 (WHO). Prerandomization work-up required CT scan of the nasopharynx, base of the skull, and cervical nodes, adequate ($\geq$ 75 ml/min creatinin clearance) renal function, normal cardiac and hematological functions, and chest x-ray, bone scintigraphy, bone marrow biopsy, liver ultrasound and/or CT scan showing no evidence of distant metastases. The patients were randomized, after giving informed consent, to receive radiotherapy alone consisting of 70 Gy in 7 weeks or 3 cycles of BEC (days 1, 21, and 42) followed 3 weeks after chemotherapy by the same radiotherapy schedule.

The BEC protocol consisted of bleomycin 15 mg IV push day 1 followed by 12 mg/m^2/day slow IV bolus day 1, cisplatinum 100 mg/m^2 over 1 h on day 1 with pre- and posthydration manitol induced diuresis, to be given every 3 weeks. A delay of 1 week was added between cycles if neutrophile counts or platelets toxicity was grade > 2 (WHO) on day 20, and CDDP was decreased to 75 mg/m^2 if calculated creatinin clearance was between 50 and 75 ml/min. Chemotherapy was discontinued if clearance was lower than 50 ml/min or if hematological toxicity was Grade 3 or more by day 35.

In both arms, the radiotherapy protocol planned to deliver 65-70 Gy in 6.5-7.5 weeks to the primary tumor, 65 Gy to clinically involved nodes, and 50 Gy to the remaining cervical and supraclavicular nodal area. The fractionation schedule used was five daily fractions of 2 Gy per week. The treatment was performed using photon beam of a ^{60}Co unit or a 4-5 MeV linear accelerator. The guidelines for irradiation of the primary site and upper cervical chain were as follows: two lateral opposed fields were used up to 42 Gy with an anterior limit of 2-3 cm in front of the pterygoid plane for T2 tumors and, depending on spread, for T3-T4; the inferior limit was above the margin of the hyoid bone; the posterior limit was generally a plane running behind the spinal apophysis; the upper limit for T2-T3 was the upper third of sphenoid sinus and above tumor spread to the base of the skull or intracranial for T4 tumors. After 42 Gy, the posterior limit was modified to exclude the spinal cord, and 28 Gy added using a reduced lateral photon fields. The

posterior fields were treated with 8 Gy if N0, and 23 Gy if palpable nodes were initially present, using 8-10 MeV electron beams.

The middle and inferior cervical nodes were treated by an anterior cervical field using photon beams of ^{60}Co or 4-5 MeV unit and the dose was specified at a depth of 3 cm. The upper limit was separated from the lower limits of the lateral fields if running through involved lymph node. The inferior limit was the upper margin of the sternum and the lateral limits were middle third of the clavicle. A systemic midline protection was used as well as subclavicular protection for the lung. In case of spinal involvement of posterior cervical nodes, two equally weighted anterior and posterior fields were used. Median follow-up was 49 months (range 23-79).

Follow-up examinations

Three months after the completion of radiotherapy, a clinical endoscopic examination, a chest x-ray and a CT scan were performed. Six months after the completion of radiotherapy, the same procedures were repeated plus a bone scan examination and a liver echography. The same procedure was then repeated in one of the two yearly follow-up visits.

Evaluation of response

Response to chemotherapy assessed at the end of every cycle and before radiotherapy were defined under WHO response criteria.[36] Response after the radiation therapy course was defined as complete if all clinically and scintigraphically detectable malignant disease had completely disappeared 3 months after the end of treatment.

Statistical analysis

The primary objective of the study was to compare overall survival at 5 years in the two treatment groups. Its secondary goal was to assess and compare the objective response rate, toxicity, and survival free of disease progression in both groups.

Results

Out of the 339 patients randomized, 171 were assigned to chemotherapy plus radiotherapy and 168 to radiotherapy only. There was no difference between the two treatment arms in the distribution of patients by tumor types. Most of the patients had T3-T4 primary tumor and N2c-N3 nodal status. The distribution of the main clinical and histological characteristics of the patients were well balanced between the two treatment groups.

Response to treatment

The response rate assessed clinically by the investigator at the completion of chemotherapy was 91% (WHO) with 47% CR and 44% PR. Three months after the completion of radiotherapy, a CR (clinical + CT scan) was observed in 55% of the combined treatment group, compared to 34% in the radiotherapy-alone group ($p<0.01$).

Tumor recurrence or progression at 4 years was observed in 55/171 (32.7%) patients in the chemotherapy arm, compared to 92/168 (54.7%) patients in the radiotherapy-alone arm ($p<0.01$).

The incidence of both, relapse and distant metastases, was reduced in the combined treatment arm. The progression-free survival at 4 years shows a statistically significant difference in favor of the chemotherapy arm. The current overall survival data are not statistically different between the two treatment modalities, but the number of events to determine its final significance has not yet been reached.

Discussion and conclusion

The most important finding of this study was the increase in progression-free survival in the combined therapy arm and the dramatic decrease in the incidence of relapse both at the primary site and at distant metastatic site.

Despite the advantage in progression-free survival, there is no survival benefit in favor of the chemotherapy arm. It is too early to report on a lack in survival difference because the initially planned number of events to show a statistically significant difference has not yet been reached.

Based on the present positive preliminary results, the International Nasopharynx Cancer Study Group has started a new trial in February 1995. With a slightly modified BEC protocol given to all patients, the patients are randomized to standard radiotherapy or to the same plus daily oral Hydroxiurea in order to reach a better local control of disease.

In conclusion, the addition of BEC type chemotherapy preceding radiotherapy has changed the proportion of UCNT patients continuously disease free. Overall survival data are not yet mature. Morbidity

and mortality are relevant problems which, when combined with radiotherapy compliance issues, make the need for close collaboration of multidisciplinary teams mandatory.

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