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Randomised Phase II Study of Methotrexate (MTX) Versus Methotrexate Plus Lonidamine (MTX + LND) in Recurrent and/or Metastatic Carcinoma of the Head and Neck

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Between March 1990 and March 1992, 89 patients with recurrent and/or metastatic squamous cell cancer of the head and neck were randomised to receive either intravenous methotrexate (MTX) at a weekly dose of 40 mg/m² plus lonidamine (LND) given orally at a starting dose of 75 mg three times daily for 3 days and then at a dose of 150 mg three times daily (arm MTX+LND) or methotrexate alone (arm MTX) at the same doses as arm MTX+LND. Complete remissions were observed in 10.5% of the patients in arm MTX+LND, and partial remissions in another 15.8%, yielding a 26.3% response rate. In arm MTX, only partial remissions were observed, yielding an overall response rate of 18.2%. Haematological toxicity was mild in both groups. Mild testicular pain (21%) and myalgias (31%) occurred only in patients treated with LND.

Key words: head and neck cancer, chemotherapy, lonidamine
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INTRODUCTION

LONIDAMINE (1-2,4-dichlorobenzyl-IH indazole-3-carboxylic acid, LND) is a new agent currently being evaluated in cancer therapy. It acts through the selective inhibition of aerobic glycolysis and oxidative phosphorylation in cancer cells. Studies with human tumour cells have shown that the combination of lonidamine with other chemotherapy agents can have an additive or even synergistic effect in human melanoma and breast cancer cells, and in head and neck squamous cell carcinoma [1–3].

In the present study, LND was administered together with methotrexate (MTX) in patients affected with recurrent and/or metastatic squamous cell cancer of the head and neck. Weekly MTX given alone, which must still be considered standard treatment for this disease at this stage, was used in the control arm.

PATIENTS AND METHODS

The study was conducted on 89 patients with squamous cell cancer of the head and neck, treated between March 1990 and March 1992 at 13 Italian hospitals. Patients was stratified according to performance status (PS) and prior treatments.

Eligibility criteria for the study included histologically confirmed, measurable, recurrent and/or metastatic squamous cell carcinoma of the head and neck, not suitable for further local therapies, age between 18 and 75 years, PS < 2 ECOG scale, white blood cells (WBC) > 3000/mm³, platelet count >100 000/mm³, no clinically meaningful heart disease, adequate liver function tests, a serum creatinine level of 120 μM/l or less, and a life expectancy of more than 3 months. After informed consent, the patients were stratified according to WHO performance status (0–1 versus 2) and prior treatments (chemotherapy/radiotherapy versus no chemotherapy/radiotherapy) then randomised to receive either intravenous (i.v.) MTX at a weekly dose of 40 mg/m² plus LND given orally at a starting dose of 75 mg three times daily for 3 days and then at a dose of 150 mg three times daily (arm MTX + LND) or MTX alone (arm MTX) at the same doses as in arm MTX+LND.

Criteria for measurable and evaluable disease and for all the assessment of response were standard WHO/UICC criteria. Standard WHO criteria for the assessment of toxicity were also used.

Toxicity was evaluated every week and response was evaluated every 4 weeks. Full blood counts and serum creatinine were measured weekly and other biochemistries every 4 weeks.

Two dose increments of 10% were scheduled for MTX in both arms if there was no toxicity after 2 weeks of treatment. Treatment was delayed until recovery in cases of grade 2 or greater myelosuppression, grade 1 or greater mucositis, or in the event of a serum creatinine increase, and resumed at reduced dosages. To evaluate response, patients had to have received at least four injections of MTX. Those requiring treatment suspension for toxicity after the first three MTX injections were considered as having progressive disease.

Sample size was planned to be initially 20 patients for each

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arm; for each response observed, 5 more patients were included up to a maximum of 20 additional patients.

RESULTS

89 patients were entered into the study. Three were ineligible: one because of a secondary primary tumour, one because of a WHO PS of 3 and another because of the presence of cerebral metastases. These patients were not included in the response and toxicity analysis.

82 patients were evaluable for response (4 patients were not: 2 refused treatment after 2 weeks, 1 for major protocol violation and 1 early death due to other causes). 85 patients were evaluable for toxicity (1 patient from arm MTX + LND was not evaluable because of major protocol violation). The patients' characteristics are shown in Table 1. The two treatment groups were well balanced with regard to all the potential prognostic factors. It should be noted that 75.6% had locoregional recurrent disease, 11.6% had both locoregional disease and distant metastases, and 12.8% presented with distant metastases only. Eighty-two per cent of the patients in arm MTX+LND and 85% in arm MTX had locoregional recurrent disease in previously irradiated areas.

The two groups were also comparable with regard to prior treatments. No patient had received prior MTX or LND. Prior chemotherapy included neoadjuvant chemotherapy with cisplatin–5-fluorouracil (11 patients), cisplatin–bleomycin (2 patients) and carboplatin–5-fluorouracil (1 patient) or concomitant chemoradiotherapy with cisplatin (8 patients) and carboplatin (1 patient) for locally advanced disease. No patient had been treated with chemotherapy for recurrent and/or metastatic disease.

Haematological toxicity was acceptable and rapidly reversible in both groups. Leucopenia occurred in 31% of the patients in arm MTX+LND and in 26% in arm MTX. Thrombocytopenia occurred in 10 and 15%, and anaemia in 31 and 20%, respectively. There was one treatment-related death from bleeding in a patient treated with MTX alone with a grade 4 thrombocytopenia.

Non-haematological toxicity consisted mainly of stomatitis, gastrointestinal toxicity such as nausea, vomiting, diarrhoea and renal toxicity.

Table 1. Patients' characteristics

Characteristics	Arm MTX+LND	Arm MTX
Male/female	35/5	43/3
Age (years)		
Median	62	62
Range	48–75	43–75
WHO performance status*		
0-1	28	31
2	11	13
Extent of disease		
Loco-regional	32	33
Metastatic	4	7
Both	4	6
Site of primary		
Oral cavity	9	9
Oropharynx	10	11
Hypopharynx	2	3
Larynx	15	18
Other	4	5
Prior treatment		
No treatment	1	3
Surgery	24	31
Radiotherapy	33	42
Chemotherapy	12	11

*Performance status unknown in 3 patients.

Table 2. Toxicity

	Arm MTX+LND	Arm MTX
Leucopenia	31(18)	26(15)
Thrombocytopenia	10(5)	15(7)
Anaemia	31(5)	20
Stomatitis	49(26)	52(17)
Cutaneous	3	4
Liver—transaminases	5	9
Nausea-vomiting	13(3)	7
Drug fever	13(3)	11
Diarrhoea	13(5)	9(2)
Renal—creatinine	10	4
Testicular pain	21(5)	0
Myalgia	31(8)	0

Values in parentheses are percentages of patients who experienced toxicity grades 3–4.

11 patients (5 MTX + LND, 6 MTX alone) had MTX dose increments.

Testicular pain and myalgias occurred only in patients treated with LND; the incidence was 21 and 31%, respectively, and was of a mild intensity in the majority of the cases. A dose reduction of LND was necessary in 2 cases and interrupted in another 2 cases. The details of the toxicity have been summarised in Table 2.

Complete remissions (CR) were observed in 4 (10.5%) of the patients treated with the MTX + LND combination, and partial remissions (PR) in another 6 (15.8%), yielding a 26.3% response rate (CR + PR; confidence interval 12.3–40.3%). Sites of responses were as follows: for complete responses, three local and one regional nodes; for partial responses, one local, two regional nodes, two local + regional nodes, one distant.

No complete responses after methotrexate alone were observed; PR were observed in 8 patients, yielding an overall response rate of 18.2% (confidence interval 6.8–29.6%). Sites of responses were as follows: three local, four regional nodes, one local + regional nodes. The median durations of the responses were 20 weeks (range 9–60) in arm MTX+LND and 13 weeks (range 4–39) in arm MTX. 8 patients in arm MTX+LND and 20 patients in arm MTX had a stable disease for a minimum of 4 weeks. 20 patients in arm MTX + LND and 16 in arm MTX had progressive disease.

The overall survival rate at 1 year was 18.3% in MTX arm and 37.4% in MTX + LND arm, with a median survival of 5 and 7 months, respectively.

The progression-free survival rate at 1 year was 5.7% in arm MTX and 16.7% in arm MTX+LND, with a median of 5 and 4.5 months, respectively.

DISCUSSION

MTX was reported to induce a 20–40% response rate in this category of patients [4]. A weekly 40–50 mg/m^2 dose of this agent is considered standard therapy; higher doses did not provide better response rates. The literature reports a wide variation in response rates obtained with this drug, probably related to the different criteria of patients selection used. For this reason, we decided in the present study to include a control arm of patients treated with MTX alone.

The EORTC Head and Neck Cancer Cooperative Group conducted a randomised phase III trial in which cisplatin

alone was compared with two different cisplatin-containing combinations [5]. The response rate to cisplatin alone was only 14%, and although the combinations produced a significantly higher response rate, the survival curves for the three treatment regimens were similar.

LND has no effect when given alone to head and neck cancer patients previously treated with radio- and chemotherapy [6]. Experimental studies have shown an additive or even a synergistic effect of LND when combined with other cytoxic agents [1–3]. Considering the peculiar action mechanisms and side-effects which do not overlap with those of standard chemotherapeutic agents, the combination of LND with chemotherapy could be of some interest.

The 26% response rate to the MTX + LND combination reported in this study was in the same range as those reported for MTX. The randomised phase II design of this trial precludes statistical comparisons between the activity of the two treatments.

Complete responses were only observed in the MTX plus LND combination arm, but the longer, if non-significant response duration, obtained with the same treatment can be attributed to a random variability in a small sample size.

The only methodologically acceptable conclusion is that both MTX and MTX plus LND have activity in recurrent and/or metastatic carcinoma of the head and neck.

A randomised phase III trial is warranted to compare the antitumour activity of these two regimens.

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Prognosis of Breast Cancer in Males: an Analysis of 170 Cases

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A statistical analysis was performed on a series of 170 consecutive cases of operable (M_0) breast cancer in males. All the patients underwent surgery. The end-points considered were: (i) overall mortality, (ii) all neoplastic events and deaths without evidence of breast disease (first event). Five- and ten-year overall mortalities were 26.9 and 54.3%, respectively. A multiple regression analysis showed that tumour size and nodal status (pT and pN) were statistically significant as prognostic factors. With regard to first events, 12 local recurrences (thoracic wall), one nodal relapse in the axilla and one contralateral tumour were observed. Primary tumours, other than breast cancer, occurred in 11 patients. The observed probability of surviving at 10 years from the treatment was definitely lower than that of the general population. For the follow-up periods of 0–5 and 6–10 years, the excess death rate per 100 man-years was 9.98 and 13.43, respectively. It appears from the analysis that prognosis of breast cancer is worse in men than in women.

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INTRODUCTION

IT WAS the aim of the present study to report our experience at the National Cancer Institute, Milan, on a series of 170 cases of operable (M_0) breast malignancies in males. Patients' survival was calculated and a statistical multivariate analysis was performed in order to evaluate the relevance of major prognostic factors, such as tumour size and axillary node metastasis. Finally, the survival probability as expected on the basis of the survival of the general population was computed, together with the excess death rate.