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Chemo-radiotherapy in the elderly and /or poor performance status patients with advanced head and neck cancer

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The aim of this study was to evaluate the toxicity and response rate, as well as to assess the impact of chemo-radiotherapy on local control and survival in the elderly and/or patients in poor performance status with head and neck squamous cell cancer (HNSCC). The treatment consisted of four cycles of induction chemotherapy with Carboplatin, Fluouracil and Leucovorin, followed by continuous infusion of Carboplatin combined with radiotherapy. Up to now, nine patients entered this study, all evaluable for toxicity and treatment response. Six patients completed the planned treatment, obtaining 2 complete responses and 2 partial responses, the other two patients remained stable during the therapy. No patient stopped the treatment due to toxicity, which was mild and limited to mucositis during radiotherapy. Due to a small number of patients and the fact that the study is still in progress we are unable to draw any definitive conclusions.

Key words: head and neck neoplasms-drug therapy-radiotherapy; aged

Introduction

In Italy, rapid aging of population is one of the most important and serious demographic phenomenon in recent years. In 1990, the average life expectancy was 73.6 years for males and 80.2 for females which is among the highest in the world.[1] In 1996, in Italy, the proportion of elderly population (over 65 years) was higher than that of young population (under 20 years). Approximately 50% of neoplastic diseases affect patients over 65 years.[1]

In elderly patients with cancer, there are often concomitant diseases that need to be considered and which limit the choice of the most appropriate cancer therapy.[2] Locoregionally advanced stage III and IV head and neck cancer has been usually treated with combined surgery and post-operative radiotherapy. Inoperable patients and those with advanced unresectable disease have been irradiated only, although the cure was achieved only in a minority of patients.[3]

Based on recent data, chemotherapy should at least be considered as an integral part of the therapy for many stage III and locally advanced stage IV patients.[4] Anticancer agents usually exhibit a relatively narrow therapeutic index leading to significant toxicity to normal tissue even at standard doses used in routine chemotherapy regimens.

Only 50% of elderly cancer patients succeed in completing the scheduled chemotherapy program at full dosage and without significant delay between courses.[5] Accurate measures of renal, liver and marrow function indexes should be considered as more important guides for the use of chemotherapy in the elderly rather than an arbitrary age limit.[5]

Carboplatin has been used in metastatic or recurrent head and neck tumors with approximately the same response rate but with less gastrointestinal and no significant chemotoxicity-ototoxicity or re-

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nal toxicity as compared with Cisplatin and has also been successfully combined with Fluouracil.[6] The interaction of Carboplatin with radiation seems more advantageous than radiation alone in lung cancer cell lines and patients.[7,8]

The present study was undertaken to establish the activity and toxicity of Carboplatin 5-fluorouracil (5FU) and Leucovorin for 4 cycles followed by Carboplatin i.v. combined with radiotherapy in elderly, inoperable HNSCC patients.

Materials and methods

From March 1996 to February 1997, 9 patients, (8 male and 1 female), of median age of 71 years (range 58-81) and a median Karnofsky Performance Status of 70 (range 60-90), with advanced, non resectable, histologically proved squamous cell carcinoma of the head and neck region, or with recurrent disease after previous primary surgery and/or radiotherapy, were recruited in the study. Three patients had stage III and 6 stage IV tumors. The primary lesion was located in the oropharynx in 6 patients, in the larynx in 1 and in the hypopharynx in 2. Informed consent was obtained from all patients.

Patients were considered eligible if they fulfilled the following criteria: inoperable disease; age over 70 and/or performance status, according to Karnofsky over 40 and under 70; a life expectancy of at least 12 weeks; absence of metastases; informed consent to treatment and follow-up; WBC count > 4,000/mm^3, PLT count > 100,000/mm^3, Hb >10 g/dl; patients with good liver function with AST, ALT, LDH, gamma-GT <2.5 times the upper limit of normal values; creatinine level < 1,2 mg/dl or creatinine clearance > 60 ml/min.

Staging was performed according to the American Joint Committee on Cancer Staging (AJCC) 1989 classification. Before entering the study, all patients underwent physical examination, and a laryngoscopy under local anesthesia. General check-up included lung and esophageal endoscopy, chest x-ray, liver echography, complete blood count and blood chemistry.

All patients received Carboplatin (AUC 3 mg/ml/min) i.v. over 1 hour, 5FU 375 mg/mq i.v. bolus, Leucovorin 100 mg/mq i.v. over 30 minutes, on day one, for a total of 4 courses, each course was repeat every two weeks.

During radiotherapy Carboplatin was adminstered at 20 mg/m^2/day, 5 days/week with a portable battery pump (Pharmacia Deltec CADD-1) connected to venous access port, recharged every week till the end of the radiotherapy treatment.

In the case of severe toxicity (> grade 2), lasting until the scheduled treatment day the course was postponed for one week. If recovery of the toxicity was still incomplete, dose modification was performed. In the case of hematologic toxicity, both drugs were reduced to 50% in granulocyte count between 1,000/μL and 2,000/μL or platelet count between 50,000/μL and 100,000/μL; in renal toxicity, the dose of Carboplatin was reduced to 75%; in mucosal toxicity, the dose of 5FU was reduced to 50% for grade > 2.

A first clinical evaluation of response was performed after the fourth chemotherapy cycle. The final evaluation was assessed by a clinical examination and a laryngoscopy under local anesthesia with biopsies for primary tumor, and by echography for neck nodes. The response was defined as progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR), according to World Health Organization (WHO) guidelines. The pathologic complete response (PCR) for primary tumor was defined as macroscopic disappearance of the lesion with negative biopsy. The response was scored separately for primary tumor and lymph nodes.

Standard external beam radiotherapy program consisted of 1.8-2.0 Gy daily fractions and a total dose of 70 Gy in seven weeks for primary lesion (T) (a 1 to 2 week split was performed when necessary) and 60 Gy to regional lymph nodes. Radiotherapy was delivered by a LINAC 6 MeV. The target volume varied according to tumor localization and stage. Whenever possible, the therapy was planned from CT scan images at several different levels. In the case of retreatment, the dose was 60 Gy (1.8 Gy/fraction) with weekly control of toxicity. Treatment fields of photons were combined with electron fields (6-15 MeV) and/or brachytherapy treatment with Ir 192 as boost.

Results

All 9 patients who entered the study, were evaluable for response to induction chemotherapy, local treatment toxicity and survival. Three patients stopped the treatment after the fourth cycle of in-

duction chemotherapy due to disease progression with worsening of the clinical condition. Six patients completed the planned treatment obtaining 2 CRs, 2 PRs and 2 SDs.

In responding patients the shrinkage of the tumor started after the second cycle of induction chemotherapy in 3, and after the first cycle in 1. All the responding patients had the primary lesion located in the oropharynx. Lymph node response was obtained only in 1 case; another patient with CR of the primary lesion is now disease free, after a neck dissection.

The toxicity of induction chemotherapy was mild without renal or liver damage, only 3 cycles were delayed by seven days to allow platelet recovery, and vomiting was observed only in 7 out of 35 cycles. During radiochemotherapy 4 patients experienced grade III mucositis and 2 grade II. The median dose of radiotherapy delivered was 61 Gy (range 60-70) in 8 weeks (range 6-10) with a median split of one week (range 0-3). One patient experienced a central catheter line thrombosis.

Up to now, 8 patients are alive, 2 without disease and 6 with persistent disease. One died two months from the start of induction chemotherapy due to neoplastic cachexia.

Discussion

With Cisplatin and 5FU infusions (PF) given for four cycles before definitive local therapy a significant survival advantage in a large subgroup of inoperable stage III and IV patients was found.[9]

More than 35% of the patients with advanced head and neck tumor, seen at our department could not be treated with PF since they did not fulfill the inclusion criteria. It is important to stress that there is no known way how to modify a curative treatment for the elderly to be associated with fewer side effects without compromising the chance for cure.

Nevertheless, renal, gastrointestinal and neural toxicities of Cisplatin limit its dosage, especially in old or debilitated head and neck cancer patients.[4] Induction chemotherapy decreases distant metastases but does not improve local disease control.[9,10] Carboplatin, besides being less toxic than Cisplatin with similar activity in head and neck patients,[6] induces potentiation of moderate-dose radiation cytotoxicity in human lung cancer cell lines.[7] It could be safely administered by continuous infusion over 6 weeks at 20 mg/m^2/day in combination with loco-regional fractionated radiation therapy 30 x 2 Gy, with mild toxicity.[8]

However, due to the small number of patients in our study, it is difficult to draw any definitive conclusion. Nevertheless, we can say that 4 cycles of Carboplatin-5-fluorouracil and Leucovorin even at low, well tolerated doses, seem to have some effect upon the tumor in elderly patients and could be followed without additional toxicity by radiotherapy with combined systemic Carboplatin infusion. The overall response in 4 out of 9 patients, with only 2 CRs is not significant. This protocol needs further evaluation, and if efficacious, it has to be compared with radiotherapy alone in a randomized study.

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