European Journal of Cancer Vol. 31A, No. 1, p. 127, 1995
Elsevier Science Ltd

0959-8049/95 $9.50+0.00

0959-8049(94)00469-2

Failure to Increase 5-Fluorouracil Activity with Interferon-α2a in the Treatment of Advanced Colorectal Cancer

A. Martoni, L. Bidin, C. Zamagni, A. Cricca and F. Pannuti

THE TREATMENT of patients with advanced colorectal cancer (CRC) is still based on the use of 5-fluorouracil (5-FU). Although lacking activity as a single agent in advanced CRC [1], interferon (IFN) has been shown to increase 5-FU antitumour activity in experimental systems [2]. On this basis, Wadler carried out a clinical study in patients with advanced CRC in which IFNα2, at a dose of 9 MU subcutaneously 3 times a week, was administered together with 5-FU at a dose of 750 mg/m^2 daily for 5 days in continuous intravenous (i.v.) infusion followed by 750 mg/m^2 weekly in i.v. bolus, obtaining an objective remission rate of 63% in 32 untreated patients [3]. This high level of activity was associated with severe toxicity and 3 patients died because of diarrhoea and leucopenia.

At our Department we carried out a phase II study on the original Wadler regimen in order to verify and confirm the possibility of modulating 5-FU therapy with IFNα2a. Thirty-one patients with measureable and/or evaluable advanced CRC entered the study from March 1991 until September 1992. Objective response and toxicity were evaluated according to WHO criteria [4]. 7 patients were not evaluable for response: 3 lost to follow-up; 2 had rapid worsening of their general condition and treatment suspended; 1 early death due to disease progression; 1 had interrupted therapy because of toxicity. 19 patients were male, 5 female, the median age was 52 (28–70) and median Karnofsky performance score (PS) was 70 (50–100). The colon/rectum was the primary site in 9/15 patients and metastases occurred in the liver (16 patients), lungs (7), abdomen and pelvis (7), bones (3), lymph nodes (1) and adrenals (1). 5 patients had received previous 5-FU chemotherapy and 2 had received radiotherapy. The median duration of the treatment was 130 days (35–348).

No complete response (CR) was observed. A partial response (PR) was obtained in two cases (8%) and minor remission (MR) (25–50% reduction of measurable lesions) in another two cases (8%). No change (NC) occurred in 9 cases (38%) and progression (P) in 10 (42%). The overall remission rate, including MR, was 17% (95% confidence limits, 5–37%). Both patients who obtained PR had lung metastases and had not received previous chemotherapy. One of the patients who had MR had lymph node metastase and pelvic recurrence. The other patient with MR had received previous 5-FU therapy. The duration of remission was 5 and 12 months for PR and 7 and 10 months for MR, respectively. The median time to progression was 3 months. All patients were evaluable for survival. Median survival was 6 months (1–19+).

Sixty-three percent of the patients (15/24) initially had symptoms, such as pain, anorexia, asthenia, but these improved in 5 patients (21%) and in all patients who demonstrated an objective response. A 10% improvement of PS occurred in 38% (9/24). A weight increase of more than 2 kg was observed in 25% (6/24).

28 patients were evaluable for toxicity. In 12, the treatment had to be suspended temporarily because of moderate but persistent leucopenia (one case because of grade 3 diarrhoea). In 3 patients, the treatment was resumed with a 30% reduction in the 5-FU dose. In one patient, treatment was withdrawn because of intolerance to IFN (severe fever and fatigue). The most frequent side-effect was a flu-like syndrome induced by IFN (68%). Leucopenia was observed in 46% (3 patients, grade 3). Transient thrombocythaemia was observed only in 2 cases, nausea-vomiting, in 11% and diarrhoea in 32%. Stomatitis of mild–moderate intensity were observed in 35%. Neurological toxicity (ataxia, memory loss and mental slackening) was reported in 3 cases (grade 3 in 1 patient).

Other authors have tried unsuccessfully to repeat the results of Wadler's study [5–8] reporting objective remission rates between 26 and 39%. At the same time, a high incidence of side effects, particularly leucopenia, diarrhoea, mucositis and neurotoxicity, were confirmed in all these studies. The remission rate obtained in our study is consistent with the findings of these "confirmatory studies". Similar to our results were those obtained with a 5-FU+AF+IFN combination which induced a remission rate of 13% in a series that included pre-treated and untreated patients [9]. The differences observed between clinical studies investigating the same problem are often the consequence of different patient selection criteria. In the present study, all consecutive patients referred to our Department were enrolled, and the inclusion of pre-treated patients and patients with a relatively low PS (50–60%) might have contributed to the modest results we obtained.

In conclusion, the addition of IFN in this study did not significantly increase antitumour activity of 5-FU. Therefore, our findings suggest that it does not have any clinical advantage compared with 5-FU alone or 5-FU + folinic acid modulation in the treatment of advanced colorectal cancer.

Correspondence to A. Martoni.
The authors are at the Divisione di Oncologia Medica, Ospedale Policlinico S. Orsola-Malpighi, via Albertoni 15, 40138 Bologna, Italia.
Revised 18 Oct. 1994; accepted 31 Oct. 1994.

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