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INTEGRATED TREATMENT WITH DOXIFLURIDINE AND RADIOTHERAPY IN RECURRENT OR PRIMARY UNRESECTABLE RECTAL CANCER. A FEASIBILITY STUDY

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Aims and background: When combined with radiotherapy, fluoropyrimidines have been shown to have synergistic effects on various tumor types. Doxifluridine (5-dFUR) is a 5-fluorouracil (5-FU) prodrug that is transformed into 5-FU in neoplastic tissue, which suggests that it may improve the activity of radiotherapy. The aims of this study were to evaluate the feasibility and efficacy of the combination of radiotherapy and oral 5-dFUR plus l-leucovorin in terms of pathologically complete remissions in locally advanced rectal cancer.

Methods: Eleven patients with locally recurrent (n = 7) or primary unresectable rectal cancer (n = 4) were treated with three cycles of oral l-leucovorin 25 mg/dose followed by 5-dFUR 750 mg/m^2 twice daily for four days every 12, in combination with pelvic radiation at a standard dose of 45 Gy over five weeks. The tumor burden was assessed by means of CT and endoscopic ultrasound at baseline and at least four weeks after the end of the treatment and before surgery.

Results: Four patients achieved an objective response, 6 disease stabilization and 1 had progressive disease. After a median time of five weeks from the end of treatment 8 patients underwent radical resection and a pathologically complete remission was documented in 2. Seven of these patients are still alive and disease free after a median follow-up of 18 months. The major side effects were grade 3 diarrhea in one case, and grade 1-2 nausea and vomiting in three cases. No significant hematological toxicity was observed.

Conclusions: This combination of radiation and 5-dFUR plus l-leucovorin led to an interesting rate of resectability, with pathological downstaging being documented in two cases. These preliminary results show an encouraging local control of an otherwise unresectable disease. Combined preoperative therapy with oral fluoropyrimidine plus l-leucovorin together with radiation may be an attractive approach in patients with operable rectal cancer.

Key words: rectal adenocarcinoma, radiotherapy, oral fluoropyrimidines.

Introduction

The treatment of rectal cancer with preoperative radiotherapy alone or combined with chemotherapy has potential advantages: firstly the possibility of better tolerance by the patients with less acute toxicity[4,10,11], and secondly the fact that the addition of chemotherapy to preoperative radiotherapy leads to downstaging and increases the resectability rate of previously unresectable tumors. Furthermore, there is no delay in starting systemic therapy, and the decrease in the volume of the primary tumor may allow the use of an otherwise impossible sphincter conserving procedure[9,12]. Recent *in vitro* and *in vivo* experiments have shown that fluorouracil has radiation sensitization effects, although their exact mechanisms have not yet been elucidated[6,7]. Doxifluridine (5-dFUR) is a fluoropyrimidine derivative whose antineoplastic activity is due to its selective conversion to 5-FU as a result of pyrimidine phosphorylases at the intracellular level[1-3]. The main advantage of 5-dFUR over 5-FU is that it is less toxic and can be administered orally.

On the basis of these considerations we designed this pilot study on the use of oral 5-dFUR plus low doses of oral l-leucovorin and pelvic radiotherapy in recurrent and/or primary unresectable rectal cancer, with the aim of assessing its feasibility, tolerability and efficacy in terms of pathologically complete remissions and local control.

Material and methods

All patients had to have histologically and cytologically confirmed advanced unresectable primary or recurrent rectal carcinoma. An unresectable tumor was clinically defined as a tumor which appeared to be fixed to an adjacent organ or structure at rectal examination. The eligibility criteria included Eastern Cooperative Oncology Group Performance Status (PS) no more than 2; leukocyte count ≥3000 mm^3/dL; hemoglobin count 9 g/dL; platelet count ≥100,000 mm^3/dL; creatinine level ≤1.5 mg/dL; and total serum bilirubin level ≤1.5 mg/dL. The study protocol was reviewed and approved by the Review Board of the Istituto Nazionale per lo Studio e

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la Cura dei Tumori. All patients gave their informed consent.

The patients were started on chemotherapy and radiotherapy on day 1. Oral l-leucovorin was administered at 25 mg/dose for four days starting two hours before 5-dFUR administration, and oral 5-dFUR was given at a dose of 750 mg/m^2 twice a day for four consecutive days starting on days 1, 13 and 25 of the treatment plan.

Megavoltage radiation therapy (15-18 MV) and multiple-field techniques (3 posterior-anterior fields and 2 lateral ones) were used. All fields were treated daily with the patient in the prone position. Techniques to minimize the toxicity of pelvic radiation were not used. The lateral border fields were 1.5 cm lateral to the widest bone margin of the true pelvic side walls, the distal border was the obturator foramen, the superior border was at the L5/S1 junction. The posterior field margin was a minimum of 1 cm behind the anterior sacral bone margin. The external iliac nodes were not treated. Radiation therapy was delivered five days a week, once daily, at 180 cGy/day. The dose was prescribed at the isocenter point. The total dose was 50.40 Gy.

Exploratory laparotomy was performed at least four weeks after the end of radiotherapy in all patients unless there was a clear demonstration of tumor progression at the end of the combined treatment. The patients who underwent radical resection received six cycles of adjuvant chemotherapy according to the preoperative schedule.

The pretreatment evaluation included physical examination, colonoscopy, abdominal/pelvic computed tomography (CT) and endoscopic ultrasound. Patterns of failure were analyzed using crude calculations, and survival by means of the Kaplan-Meier actuarial method. The data were recorded from the start of the preoperative combined treatment and all surgical specimens were pathologically examined.

Results

Between October 1994 and December 1996 11 patients with locally advanced primary (n = 4) or recurrent rectal carcinoma (n = 7) were administered the combined treatment. They were 8 males and 3 females, with a median age of 53 years (range, 43-71). All patients had a PS of 0/1; only 1 relapsed case had been previously treated with adjuvant chemotherapy.

Four of the 11 patients achieved an objective response (one CR and three PR), with the clinical remissions being equally distributed in the locally advanced and locally relapsed cases; 6 patients showed no change and 1 had local progression.

At a median of five weeks after completing the treatment, 8 of the patients underwent laparotomy. Of the three remaining cases, 1 patient with a complete response of the locally advanced primary tumor had an urethra laceration after the combined treatment which contraindicated surgical resection, and the other 2 refused.

The resection margins were negative in all 8 resected patients. Of the 3 cases in the primary locally advanced group, 2 were Dukes' pathologic stage B and 1 stage C. Two patients had no histologically identifiable residual cancer. Seven of the radically operated cases are still alive and disease free after a median follow-up of 18 months; one relapsed and died 12 months after surgery. The disease-free progression rate for all patients was 80% at one year and 60% at two years.

No grade 4 side effects were observed. Grade 1 and grade 2 nausea and vomiting were controlled by means of antiemetics. One patient with grade 3 diarrhea and tenesmus required discontinuation of chemotherapy after two cycles, but radiotherapy was completed.

Discussion

Post-resection recurrence of rectal cancer is generally fatal. A retrospective analysis of locally recurrent rectal cancer patients attending our Institution showed that only a limited number (21%) of cases with local relapses after radical surgery were amenable to surgery, and less than 10% of patients who underwent surgical exploration benefitted from secondary surgery[5].

In the present study the initial tumor in all patients was clinically adherent and/or fixed to an adjacent organ or structure. After 5-dFUR and radiotherapy, eight patients had a radical resection, two of whom showed no tumor residue in the surgical specimen.

Although we are unable to comment on the disease-free and overall survival because of the limited number of treated patients and the short median follow-up, the better local control achieved is necessarily a precursor to improve upon in these two important endpoints. Furthermore, our encouraging results appear to be as good as or better than those reported in other studies using high-dose 5-FU with radiotherapy. Some phase I and II studies on protracted venous infusion have documented a moderate increase in the incidence of severe diarrhea; the treatment also requires central venous access and an ambulatory infusion pump, which increase the complexity and cost of therapy[8,11]. The use of oral 5-dFUR should overcome this problem. The treatment was well tolerated and led to an acceptable rate of morbidity; there were no grade 4 reactions.

Any conclusions regarding the final results would be highly speculative, but the degree of local disease control and the good tolerability of the treatment make preoperative oral fluoropyrimidines plus radiation therapy an attractive approach in patients with operable rectal cancer.

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