

PREOPERATIVE TRIMODALITY TREATMENT IN ADVANCED AND RECURRENT RECTAL CANCER: A PHASE II STUDY

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Introduction

The efficacy of hyperthermia in addition to RT or chemoradiotherapy has been validated in rectal cancer. Hyperthermia has a synergetic action with both radio- and chemotherapy. Our previous experience with preoperative radiochemotherapy with 5-FU continuous infusion and hyperthermia showed good tolerance of the trimodality treatment.

Patients and Methods

From January 2001 to October 2003 forty patients entered the study ; 9 females and 31 males. Median age is 63 years (range 37-77). Patients older than 18 years, had to have an histologic diagnosis of rectal cancer and had to be chemo-naïve with a performance status of WHO 0-1. The primary lesion had to be any cT N+ or cT3-4 N0 with involvement of adjacent structures, or radial extension of more than 60% of the rectum , or axial length of the tumour greater than 3.5 cm. Relapsed rectal tumours not previously irradiated have also be included. All patients were enrolled to receive a trimodality treatment of chemotherapy with weekly oxaliplatin and 5-fluorouracil continuous infusion concomitant with radiotherapy and hyperthermia. The duration of the preoperative treatment was six weeks. After six-eight weeks from completion of treatment patients were evaluated with transrectal ultrasound and CT scan prior to surgery. The percentage of downstaging was considered as the primary aim of the study. Other end points were early and late toxicities of the preoperative treatment, the surgical complications, the percentage of conservative surgery and the percentage of resectability. Fluoracil continous infusion 200 mg/m²/die was administered throughout the duration of radiotherapy. A 20% dose reduction of 5-FU was planned in case of grade 2 neutropenia while a 50% dose reduction for grade 2 diarrhea. The infusion was discontinued for grade 3-4 neutropenia and diarrhea and for grade > 2 thrombocytopenia. L-folinic acid 100 mg/mq was administered as a 2 hours infusion before the somministration of 5-FU, no dose reduction was planned. Oxaliplatin 45 mg/mq was administered as a 2 hours infusion weekly. We planned a reduction of 50% for grade 1 thrombocytopenia and grade 2 diarrhea. For occurrence of grade 2 hand-foot syndrome a 20% dose reduction was planned. We suspended the infusion of oxaliplatin for grade ≥ 2 neutropenia, thrombocytopenia and for grade ≥ 3 diarrhea and hand-foot syndrome. Radiotherapy doses of 1,8-2,0 Gy/day, 5 days/week, for 5 weeks were delivered on the pelvis, for a total dose of 45-50.4 Gy. A boost was added on residual tumor volume during the last week, depending on the response and the side effects of treatment. The boost volume was calculated following the transrectal US or CT performed after the conventional dose. Hyperthermia has been administered weekly, in a different day from the administration of oxaliplatin, for four times at 40-45° lasting 30 minutes, by using 2000 BSD® System. Surgery has been planned after 4-6 weeks since the end of chemoradiotherapy in order to obtain the best downstaging of the primary lesion. A temporary stoma has been recommended as protection.

Results

No grade 4 side effects have been observed. Two patients experienced a grade 2 diarrhea, 2 pts presented a grade 2 proctitis and 3 pts had a moderate cystitis which did not prevent the

completion of treatment. Two patients had to discontinue oxaliplatin after the first administration because of toxicity. Surgical complications accounted for the delay of the wound healing in one patient and a perianal abscess in another patient requiring surgery. Of the 39 cases who underwent surgery, a pathological complete response has been obtained in ten patients (25.6%). A partial pathologic response has been observed in 15 patients (40%) of which 5 TmicN0M0 (12.8%). A stable disease has occurred in twelve patients (30%), of which one Tmic N+ M0. Metastatic hepatic disease has been evidenced in two patients during surgery; in one case the single secondary lesion has been surgically removed. Conservative surgery has been performed in 31(77.5%) patients, whereas a Miles approach has been necessary in 8 cases (20%). One patient who refused surgery as the post-treatment evaluation demonstrated a clinical complete response. At a median follow up of 31 months (12-53) only one (2.5%) local recurrence has been observed. Eight patients experienced distant metastasis (3 liver only, one lung only and four at multiple sites). In September 2005, 33 (82.5%) patients resulted alive, 29 (72.5%) disease-free and 4 (10%) with recurrent disease. Seven patients (17.5%) died six (15%) for progressive disease and one without evidence of cancer recurrence.