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Determination of the Optimal Dose of 5-Fluorouracil when Combined with Low Dose D,L-Leucovorin and Irradiation in Rectal Cancer: Results of Three Consecutive Phase II Studies

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In three consecutive phase II trials, 5-fluorouracil (5FU)-low dose leucovorin (20 mg/m²/day) was delivered in two 5-day courses during the first (d1 to d5) and the last (d29 to d33) week of a limited pelvic irradiation (45 Gy, 5 weeks, 25 fractions) in patients with locally extended rectal cancer. The three trials differed only by the 5FU dose in the chemotherapy (CT) schemes. In trial 1 (first CT course 5FU dose 425 mg/m²/day, second CT course 370 mg/m²/day), 16 patients were included. 5 patients suffered a grade 3+ toxicity and the compliance was 63%. In trial 2 (first and second CT course 5FU dose 370 mg/m²/day), 53 patients were included. 5 patients suffered a grade 3+ toxicity. The compliance was 94%. In the trial 3 (first and second CT course 5FU dose 350 mg/m²/day), 16 patients were included. 1 patient suffered a grade 3 toxicity and the compliance was 100%. The overall response rate (complete and partial responses) of local disease and distant metastasis were 87 and 7%, respectively. 43 patients were operated on after a mean delay of 8 weeks. Among the 41 macroscopic complete resections, 6 (14.6%) were sterilised and 12 (29.3%) were classified Asler–Coller A/B1. Regression curve analysis using either grade 3+ toxicity or incomplete treatment as an end point against the 5FU dose indicates that a 350 mg/m²/day 5FU dose is advisable for a phase III adjuvant multicentre trial.
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INTRODUCTION

IN THE treatment of advanced colorectal cancer, the biochemical modulation of 5-fluorouracil (5FU) by folinic acid (D,L-leucovorin, LV), has increased the overall response rate from 5–15% with 5FU alone up to 16–45% with the 5FU–LV association. Moreover, selected randomised studies reported an increased survival (see review [1]). Low-dose LV and 5FU significantly improved the overall survival, preferentially in patients with minimal disease [2], and was reported to be as effective as the combination of high dose LV and 5FU [3]. However, the 5FU–LV association increases the non-haematological toxicities, especially stomatitis and acute diarrhoea. The standard treatment of unresectable or locally recurrent rectal cancer is at least radiotherapy (XRT) and surgery whenever feasible [4, 5]. Delivering 5FU during XRT has been suggested to enhance the efficiency of XRT, both in the palliative and in the adjuvant setting [6, 7]. Logically, it is possible to question whether the 5-FU–LV–XRT combination may further improve the results, as predicted experimentally [8] and if the acute side-effects, mainly gastrointestinal, would be acceptable. The aims of these studies were to define, in the perspective of a multicentre phase III study, the optimal dose of 5FU in a 5FU–low dose LV–XRT combination, through three consecutive phase II trials in which the 5FU dose was the only variable, to assess the early clinical response, and to assess the pathological response for the patients operated on.

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PATIENTS AND METHODS

From February 1989 to May 1992, four centres entered 85 patients with locally extended rectal cancer into three consecutive trials (Besançon = 46, Tilburg = 24, Villejuif = 8, Dijon = 7). 16 entered the first trial (T1), 53 the second trial (T2) and 16 the third trial (T3). The pretreatment evaluation included complete physical examination, white blood count (WBC), platelet count, biological profile, chest X-ray and abdomino-pelvic computed tomography scan. Eligibility criteria were defined as an age up to 70 years, a creatinine level below 120 μmol/l, a WBC greater than 4000/ml and a platelet count greater than 130 000/ml. In T1, WHO status 0, 1 or 2 patients were eligible while entry was restriced to WHO status 0 or 1 in T2 and T3. Adenocarcinoma only were included. The tumours were classified as primarily unresectable (PU)—37 patients; locally recurrent (LR)—13 patients; gross residual after surgery (GR)—15 patients or potentially resectable (PR)—20 patients. Distant metastases were present in 22 patients. The exclusion criteria were previous chemotherapy or XRT, active infection and postoperative acute complications. Patients with distant metastasis were considered suitable for these regimens if they presented pelvic symptoms (pains, tenesmus, bleeding, etc.) uncontrolled by non-specific treatment. The detailed patient characteristics are summarised in Table 1.

Radiation therapy consideration

A photon linac beam ≥ 8 MV was used in all cases. The target volume was a limited pelvic volume designed to include 5 cm

Table 1. Characteristics of the patients in the three trials

	Trial 1	Trial 2	Trial 3
No. of patients	16	53	16
Male/female	11/5	40/13	12/4
Age (years)	62 ± 5	61 ± 10	58 ± 8
WHO status			
0	2	25	8
1	10	28	8
2	4	—	—
Tumours' characteristics			
Primarily unresectable	2	29	6
Locally recurrent	3	8	2
Gross residual	6	6	3
Potentially resectable	5	10	5
Metastasis	4	16	2

above and 5 cm below the tumour in the cephalad axis, the posterior pelvis with the entire sacrum and 3 cm beyond the macroscopic extension of the tumour anteriorly and laterally. A four portal box technique was used. The treatment was given in prone position using full bladder technique, customised shieldings were used to restrict the irradiated volume to the target volume only. A total dose of 45 Gy was planned, given in 5 weeks, 1.8 Gy per fraction, all fields treated daily. The reference dose was specified at the intersection of the axis of the beams. The target absorbed dose was at least 90% and the maximum was not higher than 105% of the reference dose (ICRU 29) [9].

Chemotherapy considerations

The 5FU–LV association was delivered in two 5-day courses during the first and the fifth or last weeks of XRT. 5FU was given as a short intravenous infusion, 1 h before XRT. LV was delivered by intravenous (i.v.) push just before 5FU. In T1, the 5FU dose for the first course was 425 mg/m^2/day and 370 mg/m^2/day for the second course, whereas the 5FU dose was the same for the two CT courses in the next studies, namely 370 mg/m^2/day in T2 and 350 mg/m^2/day in T3. In the three studies, the LV dose was 20 mg/m^2/day for the first and the second chemotherapy (CT) course. The 5FU dose was the only variable from T1 to T3.

Treatment modifications

The rules given for dose reductions at the second CT course, in case of haematological and/or gastrointestinal toxicities, are listed in Table 2. XRT was interrupted in case of grade 3 acute diarrhoea and delayed for 1 or 2 weeks. After 2 weeks rest, if severe diarrhoea was still present, XRT was permanently stopped.

Table 2.1 Dose modifications for the second chemotherapy course

Dose reductions for haematological toxicity

Toxicity WHO grade	Granulocytes per μl	Platelets per μl	Dose of drugs 5FU	LV
0	> 2000	> 100 000	100%	100%
1	1500–2000	75 000–100 000	75%	75%
2	< 1500	< 75 000	Stop permanently	

Evaluation of acute toxicities

During treatment, patients were seen twice a week, for a clinical examination and to determine WHO status, body weight and biological profile. After treatment, patients were seen weekly. Acute toxicities were scored at each visit according to the WHO acute morbidity scoring system [10]. A slightly modified scale, as indicated in Table 2, was used to score symptoms of diarrhoea.

Assessment of the response

The local tumours and distant metastases were evaluated for response after disappearance of the toxic side-effects, but not before the fifth week after completion of the treatment. An evaluation of the local tumours by digital rectal examination and computed tomography and/or endorectal ultrasound was performed in most cases. Distant metastases should be measured by ultrasound or computed tomography for hepatic lesions, and by chest X-ray for pulmonary localisation. Evaluation of the response followed the WHO recommendations for measurable and non-measurable diseases [10].

Further treatment

A surgical resection was recommended for patients having no distant metastasis. In other clinical presentations, treatment strategy was recommended according to institutional policy.

RESULTS

Toxicity

A detailed description of toxicities is given in Table 3. No toxic deaths were observed in the studies. Diarrhoea and stomatitis were more frequent than haematological toxicities. In T1, five grade 4 and three grade 3 toxicities were observed in 5 patients. A deterioration of the initial WHO status was observed in 5 patients and 4 had a weight loss ranging from 4 to 7 kg. 6 patients had an incomplete treatment, 5 in relation with a grade 2+ WBC toxicity and the other due to angina pectoris. 3 patients needed a hospital admission. The compliance with treatment in patients completing scheduled treatment was 63%. In T2, six grade 3 toxicities were observed in 5 patients. None were hospitalised. 2 patients had an incomplete treatment: 1 had the second CT course cancelled due to a pre-existent ileus and the other had a 25% dose reduction of the second CT course. The compliance with treatment was 94%. Only 1 patient in T3 had a grade 3 toxicity occurring after the end of treatment. The compliance was 100%. Grade 3+ toxicities significantly decreased from T1 to T3 ($P < 0.02$).

The time course analysis of the main observed acute toxicities demonstrated different profiles (Figs 1, 2). In T1, the WBC

Table 2.2 Dose modifications for the second chemotherapy course

Dose reductions for gastrointestinal toxicity

Toxicity WHO grade	Diarrhoea	Dose of drugs 5FU	LV
0	No	100%	100%
1	< 2 days	100%	100%
2	Tolerable > 2 days and oral treatment efficient	75%	75%
3	Oral treatment inefficient or weight loss > 10% or i.v. fluids required	Stop permanently	

Table 3. Main acute toxicities and compliance with treatment in the three trials

	Trial 1 16 patients No. of patients (%)			Trial 2 53 patients No. of patients (%)			Trial 3 16 patients No. of patients (%)		
WHO grading	2	3	4	2	3	4	2	3	4
Diarrhoea	6 (38)	2 (13)	1 (6)	8 (15)	4 (8)	0	3 (19)	1 (6)	0
Stomatitis	7 (44)	1 (6)	0	7 (13)	1 (2)	0	1 (6)	0	0
WBC	3 (19)	0	2 (13)	4 (8)	1 (2)	0	2 (13)	0	0
Platelet	3 (19)	0	2 (13)	0	0	0	0	0	0
Bladder	1 (6)	0	0	4 (8)	0	0	2 (13)	0	0
Total patients									
≥ grade 3		5 (31)			5 (9)			1 (6)	
Patients hospitalised		3 (19)			0			0	
Full treatment		10 (63)			51 (94)			16 (100)	

toxicities appeared to be higher, demonstrated a two-peak curve shape and persisted up to the tenth week. On the contrary, they appeared limited and recovered completely within 2 weeks in T2 and T3. Acute diarrhoea appeared early and persisted throughout the irradiation and further increased by the second CT course in T1 whereas they remained milder and did not demonstrate this increase in T2 and T3.

Determination of the optimal dose of 5FU

Regression curve analysis using either grade 3+ or incomplete treatment as an end point against the 5FU dose indicates that with a 350 mg/m^2/day 5FU dose one may expect a 95% rate of complete treatment or a ≈ 5% risk of grade 3 acute toxicity (Fig. 3).

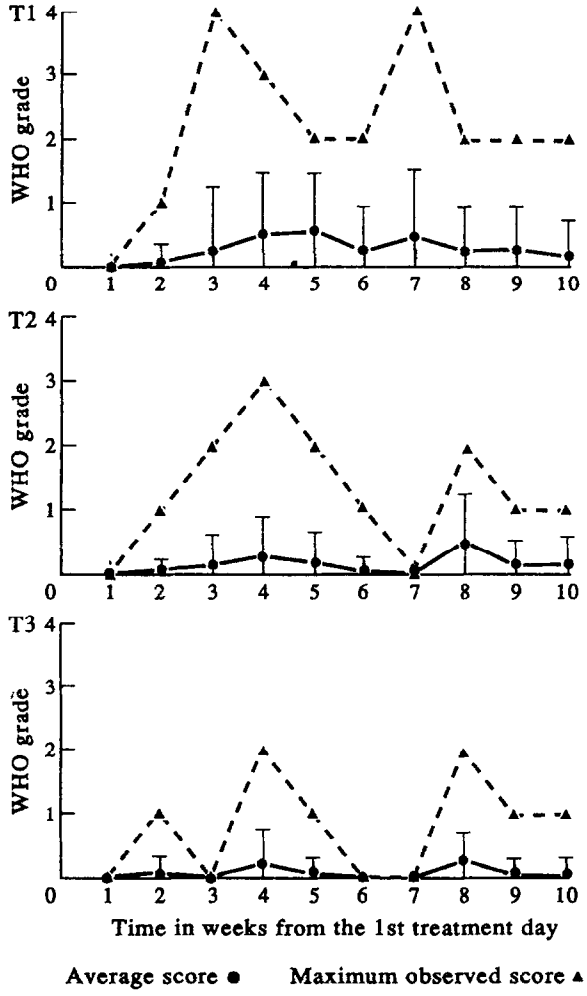

Fig. 1. Acute toxicities time course. White blood cells.

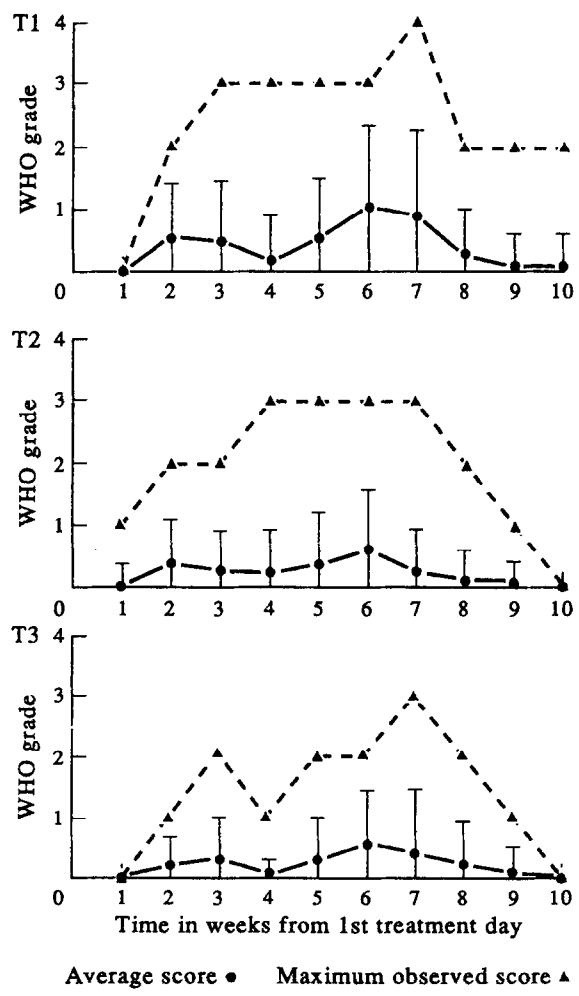

Fig. 2. Acute toxicities time course. Diarrhoea.

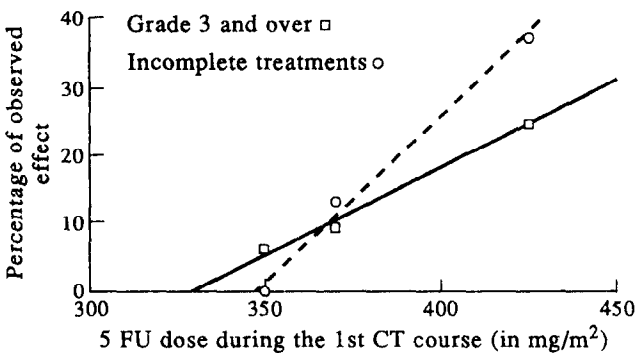

Fig. 3. 5FU dose–effect curve.

Tumour response

Among 53 patients evaluable for local response, 3 (6%) had a complete response, 43 had a partial response (81%) and 7 had no change (13%). No patient had a progressive local disease. Among 15 patients evaluable for distant response, 1 (7%) had a partial response, 9 had no change (60%) and 5 had progressive disease (33%).

Surgery

43 patients were operated on after a mean delay of 8 weeks from the treatment completion. The mean duration of the postoperative hospitalisation was 18 days (range 7–35). There was one postoperative death in a patient referred with a pre-existent ileus and a major WHO status degradation. Macroscopic complete resection was performed in 41 patients, the tumour remained unresectable in 1 patient and a macroscopic incomplete resection only was realised in 1 patient. Pathological results are summarised in Table 4.

DISCUSSION

In metastatic colorectal cancer, it has been demonstrated in a randomised trial that a 5-day combination of 5FU, 425 mg/m²/day, with low dose LV, 20 mg/m²/day, every 5 weeks, significantly increased the response rate and the survival rate when compared to 5FU alone [2].

However, severe non-haematological toxicities, especially stomatitis and diarrhoea, were increased up to 26 and 14%, respectively. The T1 scheme and doses were derived from this trial. As the combination also included a pelvic radiotherapy, the 5FU dose was reduced to 370 mg/m²/day for the second CT course to take into account the risk of increased acute severe diarrhoea. Nonetheless, the T1 results demonstrated an unacceptable rate of acute toxicities leading to a poor compliance rate. Then, in the following T2, the reduction of the 5FU dose by 20% for the first CT course obviously decreased the toxicities leading to a 94% compliance rate. Reducing further the 5FU dose to 350 mg/m² increased the compliance rate to 100%. The 5% expected grade 3 acute toxicity appeared acceptable in view of a phase III multicentre clinical trial. It is of major interest to note that the time course of the acute diarrhoea in T2 and in T3 (Fig. 2), indicates no major interaction between radiotherapy and chemotherapy on the gastrointestinal toxicities. Our approach in the determination of the optimal 5FU dose may be regarded as debatable while a pure phase I study in escalating the 5FU dose in order to determine the maximal tolerable dose (MTD) would have avoided unacceptable toxicities for some patients entered into the first trial. The pathological response in resected patients displayed apparently a dramatic down-staging of these huge tumours. More than 40% of them were classified Asler–Coller B1 or less. This may reflect a local enhancement of the radiotherapy by the concomitant chemotherapy but in the absence of randomisation it is impossible to conclude. On the contrary, the distant metastasis response rate was low, much lower than previously reported with a similar regimen [2]. However, it must be stressed that (i) it has to be considered that these were early responses only, after two courses, (ii) the evaluation was performed after a long delay without chemotherapy (average 8 weeks), and (iii) there was no formalised policy for further treatment and registration of the response. All these conditions and the small number of patients preclude any conclusion.

Table 4. Overall pathological results using Asler–Coller classification as function of the initial tumour characteristics

	Potentially unresectable	Potentially resectable	Locally recurrent
Sterilised	5	0	1
A/B1	7	4	1
B2	6	5	1
C1	1	4	—
C2	5	1	—

Reported experiences of this approach are very sparse. Minsky *et al.* [11] reported on a phase I study in 20 patients having unresectable rectal cancer. Pelvic XRT was combined with two 5-day courses of high-dose leucovorin (200 mg/m²/day) and 5FU. The first CT course was given before XRT and the second course during the fourth week of XRT. They recommended a daily 5FU dose of 250 mg/m². Mailliard [12] reported on preliminary results in 10 patients indicating that low-dose LV (20 mg/m²/day) with 5FU (400 mg/m²/day) for 3 or 4 days given during the first and last week of pelvic XRT (45–54 Gy) was feasible.

In this 5FU–LV–XRT association, the mode of administration and the optimal timing of 5FU vs. XRT and LV vs. 5FU remain to be clearly defined. *In vitro* studies using intestinal crypt cells indicated that 5FU is able to enhance the efficacy of XRT when given either before or after [13, 14]. After i.v. bolus administration of the two drugs, it has been suggested experimentally that 5FU should precede leucovorin by about 40 min in order to reach simultaneously the intratumoral peak concentrations of their respective active metabolites that are 5-fluorodeoxyuridine monophosphate and the thymidilate synthetase cofactor CH2 FH4 [15, 16].

In conclusion, the combination of a limited pelvic irradiation with 5FU–low dose LV is feasible in rectal cancer. However, to take into account the toxicity results and the regression analysis, we advise the following scheme: XRT–45 Gy in 5 weeks, 5FU–350 mg/m²/day, LV–20 mg/m²/day for two courses of 5 consecutive days delivered during the first and last week of XRT. In this setting we demonstrated that it will be possible to obtain less than 5% incomplete treatment in the perspective of a phase III multicentric study. Following these three phase II clinical studies, the EORTC cooperative radiotherapy group will initiate a phase III clinical trial in which concomitant pre-operative chemoradiotherapy will be compared to pre-operative irradiation alone in T3–T4 non-metastatic rectal cancer.

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Second Primary Neoplasms Following Breast Cancer in Saarland, Germany, 1968–1987

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A statewide cohort study on the occurrence of second primary neoplasms was conducted among 9678 women first diagnosed with breast cancer in Saarland, Germany between 1968 and 1987. A total number of 409 second primary neoplasms was observed compared to 328 cases that would have been expected based on the incidence rates of the general population (standardised incidence ratio, SIR = 1.25). This elevation in incidence of second neoplasms was primarily due to increased occurrence of cancer of the opposite breast (SIR = 2.48), which was most pronounced for patients below the age of 50 (SIR = 4.20) and within the first 5 years after diagnosis (SIR = 2.91). There was a moderate elevation in incidence of malignant tumours of the ovaries (SIR = 1.46), while the incidence of most other malignancies was lower than in the general population. Our results, which are in agreement with previous findings from Northern Europe, the U.S.A. and Japan provide valuable background information for aetiological research, as well as for surveillance of breast cancer patients.
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INTRODUCTION

STUDIES ON the occurrence of second primary neoplasms in cancer patients serve several purposes: first, these studies may suggest common (or opposite) risk factors of the first and second neoplasms [1]. Second, they may help to monitor potential adverse effects of treatment of the first malignancy, such as radiotherapy or chemotherapy [1–3]. Finally, such studies may provide guidelines for rational long-term surveillance of surviving cancer patients [1].

Overall, the occurrence of second malignancies is a rare event. As a result, the numbers of patients of single hospitals or medical centres usually provide insufficient power for epidemiological studies. Hence, the most important investigations on this topic have been contributed by population-based cancer registries, which have been set up to monitor cancer incidence and prognosis in defined large populations. This monitoring function also provides background incidence rates in the general population,

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