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# Cisplatin + 5-Fluorouracil Versus 5-Fluorouracil Alone in Advanced Colorectal Cancer: a Randomized Study

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**Abstract**—*Sixty patients with advanced colorectal cancer were randomized between cisplatin* (60 mg/mq *i.v. every* 3 *weeks*) + 5-*fluorouracil* (600 mg/mq *i.v. bolus/weekly*) *and* 5-*fluorouracil alone* (*same schedule*).

*In the* 54 *evaluable patients, no CR was observed. PR rate was* 19.2% *for the combination, and* 14.5% *for the monochemotherapy. Also the overall median survival time was similar for the two arms* (10 *and* 13 *months, respectively). Toxicity was acceptable, with more side-effects in the combination arm. Both treatments are of limited activity in advanced colorectal cancer and no advantage comes out from the use of this polychemotherapy.*

## INTRODUCTION

ADVANCED colorectal cancer is one of the less chemoresponsive neoplasms, without real improvement in the last 20 years: 5-fluorouracil (5FU) is still the reference drug, with 15–20% objective response (OR) rate. No combination of 5FU with other drugs (e.g. mitomycin C, nitrosoureas) demonstrated a reliable superiority vs. 5FU alone, either in response rate or in survival. Cisplatin (CDDP) was initially reported as active in colorectal cancer LoVo cell lines [1], while no result was achieved with this drug alone in clinical studies [2]. On the other hand, synergism between CDDP and 5FU was documented in leukaemia L1210 [3] and, in humans, in oesophageal [4, 5] and head and neck cancer [6]. These data prompted several authors to evaluate CDDP + 5FU in advanced colorectal cancer with interesting results in some studies (e.g. 32% response rate in Einhorn's experience) [7].

On the basis of these promising observations, we performed a randomized study in order to evaluate the efficacy of CDDP + 5FU in comparison to 5FU alone. Estimating the efficacy of 5FU equal to 15%, with an expected difference of 20%, for two-tailed test with alpha = 0.05 and power (1 − beta) = 0.80, the number of patients required for each treatment arm is about 80.

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## MATERIALS AND METHODS

From July 1984 to November 1986 we included in this study patients affected with advanced colorectal cancer, mostly with distant metastases and in only a few cases locally relapsed and not treatable with surgery and/or radiotherapy.

Patients with limited (<25% of parenchyma) hepatic involvement were resected and excluded from the present trial. Other eligibility criteria were: histological assessment of the primary and, whenever possible, of the metastases and/or local relapse; age <70 years; performance status (PS) <3 (ECOG); life expectancy >2 months; measurable disease; no concomitant chronic disease; no previous chemotherapy; no brain metastases; oral informed consent.

Sixty patients entered the study, 30 in the CDDP + 5FU (A), 30 in the 5FU (B) arm. Twenty-six and 28, respectively, are evaluable: their characteristics are reported in Table 1. Of the six unevaluable patients, three were 'early deaths', one was 'early progression', one was grade 3 cardiotoxicity and one was lost to follow-up after 1 month of treatment.

Patients were randomized to receive CDDP (60 mg/mq/i.v. every 3 weeks) + 5FU (600 mg/mq/i.v. bolus/weekly) or 5FU alone (same dosage). CDDP was administered in 4 h with hyperhydration, osmotic diuretics and antiemetics (steroids

*Table 1. Patient characteristics*

| | 5FU + CDDP | 5FU |
|---|---|---|
| No. of entered/evaluable patients | 30/26 | 30/28 |
| Sex (M/F) | 20/6 | 13/15 |
| Median age (range) | 53.9 (26–71) | 59.3 (40–70) |
| Performance status (ECOG): | | |
| 0–1 | 21 | 22 |
| 2–3 | 5 | 6 |
| Site of tumor: colon/rectum | 21/5 | 20/8 |
| Grading: | | |
| G1 | 33.3% | 13.6% |
| G2 | 50% | 77.3% |
| G3 | 16.7% | 9.1% |
| Median time of treatment | 3.6 months | 4.3 months |
| Site of metastases: | | |
| Liver | 54.8% | 53.2% |
| Lung | 12.9% | 15.6% |
| Peritoneum | 9.5% | 6.2% |
| Bone | 6.5% | 3.1% |
| Local | 16.2% | 21.9% |

and metoclopramide).

After three courses of CDDP + 5FU or nine doses of 5FU, patients were evaluated with repetition of the initially positive investigations (ultrasonography, CT scan, etc.), complete haematological survey and serological tumour markers (CEA, TPA, GICA). The objective response was classified according to WHO criteria. In a case of complete or partial response (CR or PR), treatment was continued until relapse, while no change (NC) patients received 4 further months of therapy and then, if OR did not improve, went off-study, as well as in case of progressive disease (PD). In a case of myelotoxicity, treatment was delayed until recovery.

## STATISTICAL METHODS

Survival from the first day of chemotherapy was analysed according to Kaplan and Meier; difference of survival curves was assessed by the log-rank test.

## RESULTS

In arm A (CDDP + 5FU) no CR was observed, while five patients (19.2%) achieved PR, with a median duration (MD) of 6 months. NC were 5 (19.2%) with a MD of 4 months and PD 16 (61.6%). Overall median survival time (MST) was 10 months (identical for the whole case-list and for the evaluable patients); responders (PR) survived 22 months, non-responders 8.

In patients treated with 5FU alone (arm B), we obtained 4 PR (14.3%), 9 NC (32.1%) and 15 PD (53.6%) with MD of 11.5+ (PR) and 5 (NC) months and MST of 15 (PR) and 12.5 (NC + PD) months. Overall MST was 13 months for the whole case-list (13.5 for the evaluable patients). No sig-

*Table 2. Toxicity (WHO criteria)*

| | CDDP + 5FU | | | | | 5FU | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | Total | 1 | 2 | 3 | 4 | Total |
| Nausea and vomiting | 7 | 5 | 5 | — | 17 | 3 | 2 | — | — | 5 |
| Leukopenia | 3 | 1 | — | — | 4 | 1 | 1 | — | — | 2 |
| Thrombocytopenia | — | 1 | — | — | 1 | 1 | — | — | — | 1 |
| Mucositis | 2 | — | 2 | 1 | 5 | 2 | 2 | — | — | 4 |
| Hair loss | — | — | — | — | — | 3 | — | — | — | 3 |
| Diarrhoea | 2 | 1 | — | — | 3 | 2 | 3 | — | — | 5 |
| Cardiotoxicity | 1* | — | 1† | — | 2 | 1‡ | 1‡ | — | — | 2 |
| Neurotoxicity | — | 1 | — | — | 1 | 1 | 1 | — | — | 2 |
| Renal toxicity | 1§ | — | — | — | 1 | — | — | — | — | — |
| Cutaneous rash | | | | | 1 | | | | | 1 |
| Other | | | | | 1‖ | | | | | 1¶ |

*Paroxistic tachycardia.
†Subendocardic ischaemia.
‡Anginous crisis.
§Creatininemia = 1.9 mg/ml.
‖Acrocyanosis.
¶Nail hyperpigmentation.

nificant difference was observed according to the base-line characteristics reported in Table 1.

No significant difference in survival curves was observed for the two arms of treatment and for all patient characteristics but patients with liver metastases showed a significant worse survival ($P = 0.0139$).

As for toxicity, we observed (Table 2) no grade 3–4 myelotoxicity; only a case of grade 4 mucositis was observed; gastroenteric side-effects (nausea and vomiting) were more evident for CDDP + 5FU, even though no grade 4 case was registered. Four patients, two for each arm, experienced cardiotoxicity, possibly drug related. In the CDDP + 5FU arm, one patient showed grade 1 nephrotoxicity.

## DISCUSSION

The different response rate between CDDP + 5FU and 5FU alone turned out to be 5% (−15% and 25%, as lower and upper, 95% confidence limits). Taking into account the toxicity of CDDP, the practical problems related to its administration, and that with 30 patients per arm we are reasonably sure we would not have missed a clinically relevant (about 50%) reduction in failure of the CDDP + 5FU, we decided to stop the study [8].

This experience indicates that, with these doses and schedule, CDDP + 5FU is not superior to 5FU alone in advanced colorectal cancer. Our data are in agreement with the recent update by Loehrer *et al.* [9]: in a randomized study, comparing CDDP + 5FU (same schedule as in our study) with 5FU, they report, in 110 patients, a similar activity for both treatments (19% and 18% ORs).

Moreover, a randomized study of 101 patients performed by the EORTC Gastrointestinal Cancer Group, comparing 5FU + CDDP + allopurinol vs. 5FU alone, showed a superimposable efficacy for the two treatments: CR + PR = 15.8% and 13.6% respectively [10].

Toxicity was less evident, in our experience, than in other trials but this fact did not affect the activity of the combination.

Perhaps, the association between CDDP and 5FU could be re-evaluated with modifications of the schedule: 5FU given by continuous infusion with pulses of weekly CDDP appeared promising in Cantrell *et al.*'s experience [11], even though at least one more recent report [12] indicates lower efficacy.

For the moment, no clear-cut superiority for CDDP + 5FU can be assessed and no recommendation for its use in clinical practice can be made.

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