Alpha-interferon does not increase the efficacy of 5-fluorouracil in advanced colorectal cancer

Meta-Analysis Group in Cancer

Summary Two meta-analyses were conducted to quantify the benefit of combining α-IFN to 5FU in advanced colorectal cancer in terms of tumour response and survival. Analyses were based on a total of 3254 individual patient data provided by principal investigators of each trial. The meta-analysis of 5FU ± LV vs. 5FU ± LV + α-IFN combined 12 trials and 1766 patients. The meta-analysis failed to show any statistically significant difference between the two treatment groups in terms of tumour response or survival. Overall tumour response rates were 25% for patients receiving no α-IFN vs. 24% for patients receiving α-IFN (relative risk, RR = 1.02), and median survivals were 11.4 months for patients receiving no α-IFN vs. 11.5 months for patients receiving α-IFN (hazard ratio, HR = 0.95). The meta-analysis of 5FU + LV vs. 5FU + α-IFN combined 7 trials, and 1488 patients. This meta-analysis showed an advantage for 5FU + LV over 5FU + α-IFN which was statistically significant in terms of tumour response (23% vs. 18%; RR = 1.26; P = 0.042), and of a borderline significance for overall survival (HR = 1.11; P = 0.068). Metastases confined to the liver and primary rectal tumours were independent favourable prognostic factors for tumour response, whereas good performance status, metastases confined to the liver or confined to the lung, and primary tumour in the rectum were independent favourable prognostic factors for survival. We conclude that α-IFN does not increase the efficacy of 5FU or of 5FU + LV, and that 5FU + α-IFN is significantly inferior to 5FU + LV, for patients with advanced colorectal cancer. © 2001 Cancer Research Campaign

Keywords: 5-fluorouracil; interferon; colorectal cancer; meta-analysis

The outcome of patients with non-operative metastatic colorectal cancer remains poor. Four meta-analyses previously performed by the Meta-Analysis Group In Cancer confirmed that the effect of intravenous bolus 5-fluorouracil (5FU) can be increased by the modulation of 5FU by leucovorin (Advanced Colorectal Cancer Meta-analysis Project 1992) or by methotrexate (Advanced Colorectal Cancer Meta-analysis Project 1994), the administration of 5FU by continuous infusion (Meta-Analysis Group in Cancer 1998), or the administration of fluoropyrimidines through the hepatic artery (Meta-Analysis Group in Cancer 1996) in case of metastases confined to the liver. Each meta-analysis showed a large increase in tumour response, without substantial impact on survival.

In the late 1980s, alpha-interferon (α-IFN) was proposed to increase the efficacy of 5FU in advanced colorectal cancer. After the initial report by Wadler et al (1989) of a tumour response rate of 76% in a group of 17 previously untreated patients, additional phase II trials of 5FU plus α-IFN with or without leucovorin were undertaken (Pazdur et al, 1990); (Piedbois et al, 1991); (Weh et al, 1992); (Raderer and Scheithauer, 1995) followed by several randomized phase III trials. Most randomized trials were disappointing, but despite a total of 3500 patients enrolled in these studies, there is to date no overall assessment of the true impact of α-IFN in advanced colorectal cancer. We therefore decided to explore this question through a meta-analytic approach based on individual patient data. Toxicity was not studied, since at the time of beginning the present analyses, individual trials had already demonstrated that the addition of α-IFN to a 5FU regimen led to an increased risk of toxicity.

Writing Committee: Pierre Thirion, Pascal Piedbois, Marc Buyse, Peter J. O’Dwyer, David Cunningham, Anthony Man, Frank A. Greco, Giuseppe Colucci, Claus-Henning Köhne, Francesco Di Costanzo, Andrea Piga, Sergio Palmeri, Patrick Dufour, Allessandra Cassano, Gabor Pajkos, Raul Pensel, N. Faruk Aykan, John Marsh, Matthew T. Seymour

Collaborators: Peter J. O’Dwyer, Louise Ryan, Judith Manola (Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, USA), David Cunningham, Andy Norman (The Royal Marsden Hospital, Sutton, United Kingdom), Matthew T. Seymour, Richard J. Stephens, (Medical Research Council, United Kingdom), Giuseppe Colucci (Gruppo Oncologico dell’Italia Meridionale, Italy), Claus-Henning Köhne, Hans-Joachim Schnoll, (Arbeitsgemeinschaft Internistische Onkologie, Germany), Francesco Di Costanzo (Gruppo Oncologico Italiano di Ricerca Clinica, Italy), Andrea Piga (University of Ancona, Italy), Sergio Palmeri, (University of Palermo, Italy), Patrick Dufour (Hôpital de Hautepierre, Strasbourg, France), Allessandra Cassano, Carlo Barone, (Università Catolica S. Cuore, Roma, Italy), Anthony Man (Novartis Pharma, Basel, Switzerland), Frank A. Greco (Sarah Cannon Cancer Center, Nashville, TN, USA), Lawrence Einhorn, (Indiana University Cancer Center, Indianapolis, USA), Gabor Pajkos (MI Central Hospital, Budapest, Hungary), Gyorgy Bodoky (National Institute of Oncology, Budapest, Hungary), Raul Pensel (Hospital Municipal Jose M. Penna, Buenos Aires, Argentina), N. Faruk Aykan, (Istanbul University, Turkey, John Marsh (Yale University School of Medicine, New Haven, CT, USA), Peter Sorensen (Aarhus University Hospital, Aarhus, Denmark), Kosmidis (Hellenic Cooperative Oncology Group, Greece), Francesco Recchia (Istituto Oncologico Regionale Abruzzo e Molise, Italy), Pierre Thirion (St. Luke’s Hospital, Dublin, Ireland), Yoriu Piedbois, Eric Gauthier, Anne-Chantal Braud, Alain Piatot (European Association for Research in Oncology, Creteil, France), Pascal Piedbois (Henri Mondor Hospital, Assistance Publique de Paris, Creteil, France), Marc Buyse, Emmanuel Quinaux (International Drug Development Institute, Brussels, Belgium)

Board of the Meta-Analysis Group In Cancer: Norman Wolmark (Pittsburgh, PA, USA) (President), Pascal Piedbois, MD (Creteil, France) (Secretary), Marc Buyse, ScD (Brussels, Belgium) (Statistician), Charles Erlichman, MD (Rochester, MN, USA), Robert Carlson, MD (Stanford, CA, USA), Youssef Rustum, PhD (Buffalo, NY, USA).
METHODS

Trial selection

Two meta-analyses were conducted concomitantly. In the first one, we considered all properly randomised trials comparing 5FU with or without folinic acid (5FU ± LV) to the same 5FU ± LV regimen plus α-IFN (5FU ± LV + α-IFN). In the second meta-analysis we considered all properly randomised trials comparing 5FU + LV to 5FU + α-IFN. In both meta-analyses, α-IFN must have consisted of α-2a-interferon or α-2b-interferon, and patients must have been included in the trial before July 1996. The search for relevant trials was initiated in October 1996 by consulting MEDLINE, Physician Data Query (PDQ), the proceedings of major conferences since 1989, and through contacts with principal investigators. A total of 20 relevant trials were identified, but 3 of them (335 patients) could not be included in the meta-analysis, due to lack of data or information on the trial (Kreuser et al, 1995); (Kosmidis et al, 1996); (Recchia et al, 1996).

Meta-analysis of 5FU ± LV vs. 5FU ± LV + α-IFN (Table 1)

The comparison of 5FU versus 5FU + α-IFN was addressed in 7 trials, the Roche International Clinical Research Center (RICRC) trial (Greco et al, 1996), the Palermo trial (Palmeri et al, 1998), the Ancona trial (Piga et al, 1996), two Royal Marsden Hospital (RMH) trials (Hill et al, 1995a+b), the trial from France (Dufour et al, 1996), and the Eastern Cooperative Oncology Group, Cancer and Leukemia Group B (ECOG/CALGB) trial (O’Dwyer et al, 1996). The ECOG/CALGB trial (O’Dwyer et al, 1996) was not considered in the first meta-analysis, because unlike the other trials, the planned dose of 5FU and its mode of administration were not the same in the 2 treatment groups. In most trials, the 5FU regimen was close to the Wadler regimen (Wadler et al, 1989), consisting of an initial 5-day 5FU infusion followed by a weekly 5FU infusion. The dose of 5FU varied from 500 to 750 mg/m²/day. The dose of α-IFN varied from 3 to 10 MU, 3 times a week. Based on the impact of the mode of 5FU administration on tumour response and survival (Meta-Analysis Group In Cancer, 1992), we decided to pool the results from these trials.

Table 1: Randomised clinical trials comparing 5FU ± LV to 5FU ± LV + α-IFN in advanced colorectal cancer

| Comparison          | Patients | Treatment arms                                                                 |
|---------------------|----------|-------------------------------------------------------------------------------|
| 5FU vs. 5FU + α-IFN, with 5FU bolus |          |                                                                                |
| RICRC               | 245      | 5FU 750 mg/m²/d continuous infusion d1 to d5, then weekly on bolus             |
| Greco et al, 1996   |          | Same + α-IFN 9 MU three times a week                                            |
| Palermo             | 169      | 5FU 750 mg/m²/d bolus d1 to d5; then weekly                                   |
| Palmeri et al, 1998 |          | Same + α-IFN 9 MU three times a week                                            |
| Ancona              | 141      | 5FU 500 mg/m²/d bolus d1 to d5; then weekly                                   |
| Piga et al, 1996    |          | Same + α-IFN 3 MU/d                                                           |
| RMH                 | 106      | 5FU 750 mg/m²/d continuous infusion d1 to d5; then weekly on bolus             |
| Hill et al, 1995a   |          | Same + α-IFN 10 MU three times a week                                          |
| France              | 106      | 5FU 750 mg/m²/d continuous infusion d1 to d5; then weekly on bolus             |
| Dufour et al, 1996  |          | Same + α-IFN 9 MU three times a week                                           |

| Comparison          | Patients | Treatment arms                                                                 |
|---------------------|----------|-------------------------------------------------------------------------------|
| 5FU vs. 5FU + α-IFN, with 5FU continuous infusion |          |                                                                                |
| RMH PVI             | 160      | 5FU 300 mg/m²/d continuous infusion d1 to d70 followed by a 2 week-break      |
| Hill et al, 1995b   |          | Same + α-IFN 5 MU three times a week                                           |

| Comparison          | Patients | Treatment arms                                                                 |
|---------------------|----------|-------------------------------------------------------------------------------|
| 5FU + LV vs. 5FU + LV + α-IFN, with 5FU bolus |          |                                                                                |
| GOIM                | 204      | 5FU 375 mg/m²/d bolus d1 to d5, + l-folinic acid 100 mg/m²/d bolus d1 to d5 every 3 weeks |
| Colucci et al, 1999 |          | Same + α-IFN 3 MU/d d-2 to d5                                                  |
| Roma                | 148      | 5FU 370 mg/m²/d bolus d1 to d5, + l-folinic acid 80 mg/m²/d bolus d1 to d5 every 4 weeks |
| Cassano et al, 1996 |          | Same + α-IFN 3 MU 3 times a week                                                |
| Hungary             | 73       | 5FU 425 mg/m²/d bolus d1 to d5 LV 20 mg/m²/d d1 to d5 every 4 weeks             |
| Pajkos et al, 1997  |          | Same + α-IFN 3 MU 3 times a week                                                |
| Argentina           | 55       | 5FU 600 mg/m²/d bolus d1 to d5 + LV 500 mg/m²/d bolus d1 to d5 every 3 weeks    |
| Pensel et al, 1993  |          | Same + α-IFN 5 MU/d, d1 to d5 every 3 weeks                                    |

| Comparison          | Patients | Treatment arms                                                                 |
|---------------------|----------|-------------------------------------------------------------------------------|
| 5FU + LV vs. 5FU + LV + α-IFN, with 5FU continuous infusion |          |                                                                                |
| MRC                 | 260      | 5FU 800 mg/m²/d, (bolus + continuous infusion) d1 and d2, + LV 200 mg/m²/d bolus d1 and d2 every 2 weeks |
| Seymour et al, 1996 |          | Same + α-IFN 6 MU every other day d1 to d12                                    |
| AIO                 | 99       | 5FU = 2 600 mg/m²/d IVC + LV = 500 mg/m²/d bolus, every week                   |
| Köhne et al, 1998   |          | same + IFN = 3 MIU/d, 3d/w                                                       |
Randomised clinical trials comparing 5FU + LV to 5FU + α-IFN in advanced colorectal cancer

The comparison of 5FU + LV versus 5FU + LV + α-IFN was addressed in 6 trials, the Gruppo Oncologico dell’Italia Meridionale (GOM) trial (Colucci et al, 1999), the Roma trial (Cassano et al, 1996), the trial from Hungary (Pajkos et al, 1997), the trial from Argentina (Pensel et al, 1993), the Medical Research Council (MRC) trial (Seymour et al, 1996), and the AIO trial (Köhne et al, 1998). The AIO trial (Köhne et al, 1998) and the trial from Hungary (Pajkos et al, 1997) were multiple-arm trials. Two trials (MRC (Seymour et al, 1996), AIO (Köhne et al, 1998)) used a continuous infusion 5FU. Trials were stratified according to 5FU schedule of administration (5FU bolus and 5FU continuous infusion), and in terms of modulation of 5FU by leucovorin.

Meta-analysis of 5FU + LV vs. 5FU + α-IFN (Table 2)

The comparison of 5FU + LV versus 5FU + α-IFN was addressed in 7 trials, the Corfu-A trial (Corfu-A Study Group, 1995), the GOIRC trial (Di Costanzo et al, 1995), the Yale trial (Marsh et al,), the trial from Turkey (Aykan et al, 1996), the ECOG/CALGB trial (O’Dwyer et al, 1996), the AIO trial (Köhne et al, 1998), the trial Hungary (Pajkos et al, 1997). Three of these trials (O’Dwyer et al, 1996; Pajkos et al, 1997; Köhne et al, 1998) were multiple-arms trials.

In 4 trials same 5FU schedules were used in the 5FU/LV and in the 5FU+IFN arms: 5FU bolus in the GOIRC (Di Costanzo et al, 1995), the Hungary (Pajkos et al, 1997), and the Turkey (Aykan et al, 1996) trials, and 5FU continuous infusion in the AIO (Köhne et al, 1998). In the 3 remaining trials (Corfu-A Study Group, 1995; (Marsh et al) (O’Dwyer et al, 1996) 5FU consisted of bolus injection in the 5FU/LV arm, and of continuous infusion in the 5FU+IFN arm. Trials were therefore stratified according to 5FU administration, i.e. same 5FU schedules in both arms (Di Costanzo et al, 1995; Aykan et al, 1996, Pajkos et al, 1997; Köhne et al, 1998) were multiple-arms trials.

Table 2

| Comparison | Patients | Treatment arms |
|------------|----------|----------------|
| 5FU + LV vs. 5FU + α-IFN, with the same dose of 5FU in both arms |
| GOIRC | 238 | 5FU 600 mg/m² bolus, + l-folinic acid 250 mg/m² bolus, + HU 3 g once a week for 6 weeks followed by a 2 week-break |
| Di Costanzo et al, 1995 | 5FU 600 mg/m² bolus, + l-folinic acid + l-folinic acid + α-IFN 3 MU three times a week |
| AIO | 187 | 5FU 2 600 mg/m² continuous infusion + LV 500 mg/m² bolus, once a week for 6 weeks followed by a 2 week-break |
| Köhne et al, 1998 | Same without LV + α-IFN 3 MU three times a week |
| Turkey | 46 | 5FU 500 mg/m²/d bolus d1 to d5 + l-folinic acid 100 mg/m², then weekly, every 4 weeks |
| Aykan et al, 1996 | Same without l-folinic acid + IFN 5 MU three times a week |

| Comparison | Patients | Treatment arms |
|------------|----------|----------------|
| 5FU + LV vs. 5FU + α-IFN, with a higher dose of 5FU in the 5FU + α-IFN arm |
| Corfu-A | 496 | 5FU 370 mg/m²/d bolus, + LV 200 mg/m²/d d1 to d5 every 4 weeks |
| Corfu-A Study Group, 1995 | 5FU 750 mg/m²/d continuous infusion d1 to d5, then weekly on bolus + α-IFN 9 MU three times a week |
| ECOG/CALGB | 443 | 5FU 600 mg/m²/d bolus + LV 600 mg/m² bolus once a week |
| O’Dwyer et al, 1996 | 5FU 750 mg/m²/d continuous infusion d1 to d5, then weekly on bolus + α-IFN 9 MU three times a week |
| Hungary | 69 | 5FU 425 mg/m²/d bolus d1 to d5 LV 20 mg/m²/d d1 to d5 every 4 weeks |
| Pajkos et al, 1997 | 5FU 750 mg/m²/d bolus d1 to d5 every 4 weeks + IFN 3 MU three times a week |
| Yale | 9 | 5FU 425 mg/m²/d bolus d1 to d5, + LV 20 mg/m²/d d1 to d5 every 4 weeks |
| Marsh et al | 5FU 750 mg/m²/d continuous infusion d1 to d5, then weekly on bolus + α-IFN 9 MU three times a week |

Protocol for the meta-analysis

In March 1997, all principal investigators received a protocol for the meta-analyses, and were asked to provide individual patient data. Information requested for every randomised patient was date of randomisation, tumour measurability (i.e. measurable or non-measurable tumours), treatment assigned by randomisation, age, gender, performance status according to the ECOG scale, primary tumour site (colon or rectum), prior adjuvant chemotherapy, prior chemotherapy for metastatic disease, site of metastases, overall response status with the first assigned treatment, date of response or progression with the first allocated treatment, cross-over to another treatment arm, date of death or last visit, survival status, and cause of death if applicable. Data on toxicity were not collected.

Data collection

All individual patient data were received by April 1999. Data were extensively checked and discussed with all collaborators present at a plenary meeting of the Meta-Analysis Group In Cancer held in Atlanta, GA, in May 1999.

Tumour response and survival

Complete response (CR) and partial response (PR) criteria adopted in individual trials followed the World Health Organization recommendations (Miller et al, 1981) and were similar in all trials. Patients experiencing minimal response, stable disease or progressive disease were considered to have no response for the purpose of the meta-analyses. In the MRC trial (Seymour et al, 1996) and in the trial from Hungary (Pajkos et al, 1997) chemotherapy was stopped after 6 months in the absence of tumour progression. In all
other trials treatment was maintained until disease progression or severe toxicity. Duration of survival was calculated from the date of randomisation to the date of death, whatever its cause.

**Statistical methods**

The statistical methods for meta-analyses based on individual patient data have been described in detail in previous publications (ACCMP, 1992; ACCMP, 1994; MAGIC, 1996; MAGIC, 1998a; MAGIC, 1998b). All analyses were based on an intention to treat basis, without any patient exclusion. Tumour responses were compared through relative risks (RR) in individual trials and overall (MAGIC, 1998b). Prognostic factors for response were identified through a logistic regression model (Cox, 1970). Survival times were compared through hazard ratios (HR) in individual trials and overall (Peto et al, 1977). Prognostic factors for survival were identified through a proportional hazards regression model (Cox, 1972). All P values were two-sided.

**RESULTS**

**Patient characteristics**

A total of 3254 were included in the analyses. The main patient characteristics are listed in Table 3 and 4. As could be expected in large series of patients, there was no imbalance between the experimental and the control groups for either of the comparisons of interest. 84% of patients had died at the time of analysis.

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### Table 3 Patient characteristics: 5FU+/−LV vs. 5FU+/−LV+IFN

| Trial     | Accrual period | Trt. | No. of patients | Adjuvant chemo. (%) | Primary colon (%) | PS=2 (%) | Metastases (%) | Liver only | Lung only |
|-----------|----------------|------|-----------------|---------------------|------------------|----------|----------------|------------|----------|
| RICRC     | 1989–92        | 5FU  | 124             | 0                   | NA               | 83       | 62             | 9          |          |
| Greco et al, 1996 | 5FU+IFN | 121 | 0               | NA                  | 92               | 63       | 4             |          |          |
| Palermo 1990–93 | 5FU   | 88  | 0               | 100                 | 95               | 62       | 3             |          |          |
| Palermo et al, 1998 | 5FU+IFN | 81  | 0               | 100                 | 97               | 61       | 0             |          |          |
| Ancona 1990–93 | 5FU   | 72  | 3               | 75                  | 97               | 44       | 6             |          |          |
| Piga et al, 1996 | 5FU+IFN | 69  | 3               | 72                  | 97               | 48       | 6             |          |          |
| RMH 1990–92 | 5FU   | 54  | 0               | 63                  | 87               | 28       | 2             |          |          |
| Hill et al, 1995a | 5FU+IFN | 52  | 0               | 71                  | 77               | 19       | 13            |          |          |
| France 1990–93 | 5FU   | 50  | 0               | 73                  | 100              | 52       | 6             |          |          |
| Dufour et al, 1996 | 5FU+IFN | 56  | 0               | 73                  | 100              | 48       | 11            |          |          |
| RMH PVI 1992–94 | 5FU   | 80  | 0               | 81                  | 58               | 19       | 9             |          |          |
| Hill et al, 1995b | 5FU+IFN | 80  | 0               | 70                  | 60               | 19       | 9             |          |          |
| GOIM 1991–94 | 5FU+LV | 101 | 0               | 56                  | 88               | 41       | 7             |          |          |
| Colucci et al, 1999 | 5FU+LV+IFN | 103 | 1               | 66                  | 95               | 40       | 2             |          |          |
| Roma 1990–96 | 5FU+LV | 73  | 0               | 67                  | 79               | 17       | 3             |          |          |
| Cassano et al, 1996 | 5FU+LV+IFN | 75  | 0               | 71                  | 81               | 10       | 3             |          |          |
| Hungary 1993–96 | 5FU+LV | 35  | 0               | 47                  | 74               | 60       | 0             |          |          |
| Pajkos et al, 1997 | 5FU+LV+IFN | 38  | 0               | 66                  | 76               | 39       | 3             |          |          |
| Argentina 1990–91 | 5FU+LV | 28  | 0               | 61                  | 57               | 43       | 0             |          |          |
| Pensel et al, 1993 | 5FU+LV+IFN | 27  | 0               | 59                  | 59               | 41       | 7             |          |          |
| MRC 1991–93 | 5FU+LV | 132 | 1               | 69                  | 74               | 43       | 3             |          |          |
| Seymour et al, 1996 | 5FU+LV+IFN | 128 | 1               | 67                  | 76               | 36       | 5             |          |          |
| AIO 1992–93 | 5FU+LV | 50  | 10              | 46                  | 94               | 34       | 0             |          |          |
| Köhne et al, 1998 | 5FU+LV+IFN | 49  | 6               | 51                  | 96               | 44       | 4             |          |          |
| Total 1989–96 | 5FU+/−LV | 887 | 1               | 70                  | 98               | 43       | 5             |          |          |
| 5FU+/−LV+IFN | 879 | 1       | 71             | 98               | 40               | 5         |                |          |          |

NA = not available.
administration. Median survivals were 11.4 months for patients treated without α-IFN, and 11.5 months for patients treated with α-IFN.

Meta-analysis of 5FU + LV vs. 5FU + α-IFN

1488 patients were included in this meta-analysis. The ECOG/CALGB trial (O’Dwyer et al 1996) allowed the inclusion of patients with non-measurable disease. After exclusion of these patients, 1305 patients were eligible for tumour response assessment.

Tumour response rates were 23% (152/655) for patients allocated to 5FU + LV vs. 18% (115/650) for patients allocated to 5FU + α-IFN. The overall tumour response RR was 1.26 (95% CI = 1.01–1.59; \( P = 0.042 \)), showing a statistically significant advantage for 5FU + LV over 5FU + α-IFN (Figure 3). However, the heterogeneity between trials in this meta-analysis was rather important (\( P \) value for heterogeneity, \( P = 0.001 \)), mostly between trials using the same 5FU schedules in both treatment arms (\( P \) value for heterogeneity, \( P = 0.003 \)).

Analyses stratified by type of 5FU administration showed that the advantage of 5FU + LV over 5FU + α-IFN was limited to the group of trials using the same 5FU schedules in both treatment arms (RR = 1.80; 95% CI = 1.29–2.51; \( P = 0.0005 \)).

Survival analysis showed a small trend in favour of 5FU + LV over 5FU + α-IFN, but this advantage was not statistically significant (overall HR = 1.11; 95% CI = 1.07–1.25; \( P = 0.005 \) (Figure 4). Median survivals were 11.7 months for patients allocated to 5FU + LV and 11.3 months for patients allocated to 5FU + α-IFN. The survival difference reached statistical significance in the group of trials using the same 5FU schedules in both treatment arms (HR = 1.29; 95% CI 1.07–1.57; \( P = 0.008 \)). There was some heterogeneity in this group of trials, but which did not reach a statistically significant level (\( P = 0.67 \)).

Prognostic factor analyses

Individual patient data used for the two meta-analyses were combined to identify prognostic factors for response and survival (3254 patients). Sex, age, performance status (PS), primary tumour site, previous adjuvant chemotherapy, metastatic site, and allocated treatment (no α-IFN vs. α-IFN) were considered in these analyses. In a logistic regression model, metastases confined to the liver (\( P < 10^{-4} \)), and primary rectal tumours (\( P = 0.042 \)) were the independent favourable prognostic factors for tumour response. Tumour response rates were 26% for patients with metastases confined to the liver versus 20% for the others. Patients with rectal cancer had a 26% tumour response rate, vs. 22% with colon tumour.

**Table 4** Patient characteristics: 5FU±LV vs. 5FU±IFN

| Trial            | Accrual Period | Trt. | No.of Patients | Adjuvant Chemo. (%) | Primary colon (%) | PS<2 (%) | Metastases (%) |
|------------------|----------------|------|----------------|---------------------|------------------|----------|----------------|
| Corfu-A         | 1989–91        | 5FU/LV | 250            | 0                  | NA               | 83       | 38             |
| Corfu-A Study Group, 1995 | 5FU+IFN | 246 | 0 | NA | 83 | 37 | 4 |
| ECOG            | 1990–95        | 5FU/LV | 224            | 12                  | 68               | 92       | 37             |
| O’Dwyer et al, 1996 | 5FU+IFN | 219 | 11 | 73 | 95 | 35 | 9 |
| AIO             | 1992–95        | 5FU/LV | 93             | 12                  | 50               | 96       | 44             |
| Köhne et al, 1998 | 5FU+IFN | 94 | 11 | 61 | 92 | 39 | 7 |
| GOIRC           | 1992–94        | 5FU/LV | 119            | 0                  | 64               | 98       | 56             |
| Di Costanzo et al, 1995 | 5FU+IFN | 119 | 0 | 59 | 97 | 59 | 5 |
| Hungary         | 1993–96        | 5FU/LV | 35             | 0                  | 47               | 74       | 60             |
| Pajkos et al, 1998 | 5FU+IFN | 34 | 0 | 53 | 79 | 50 | 3 |
| Turkey          | 1992–94        | 5FU/LV | 19             | 15                  | 50               | 72       | 21             |
| Aykan et al, 1996 | 5FU+IFN | 27 | 15 | 21 | 62 | 37 | 11 |
| Yale            | 1990–91        | 5FU/LV | 4              | 0                  | 75               | 100      | 25             |
| Marsh et al     | 5FU+IFN        | 5              | 0      | 100  | 80 | 60 | 0 |
| Total           | 1989–96        | 5FU/LV | 744           | 6                   | 61               | 89       | 42             |
|                 | 5FU+IFN        | 744        | 5       | 64   | 89 | 41 | 6 |

NA = not available.

Figure 1 Tumour response relative risks in individual trials and overall for the meta-analysis 5FU ± LV vs. 5FU ± LV + α-IFN

Tumour response rates were 23% (152/655) for patients allocated to 5FU + LV vs. 18% (115/650) for patients allocated to 5FU + α-IFN. The overall tumour response RR was 1.26 (95% CI = 1.01–1.59; \( P = 0.042 \)), showing a statistically significant advantage for 5FU + LV over 5FU + α-IFN (Figure 3). However, the heterogeneity between trials in this meta-analysis was rather important (\( P \) value for heterogeneity, \( P = 0.001 \)), mostly between trials using the same 5FU schedules in both treatment arms (\( P \) value for heterogeneity, \( P = 0.003 \)).

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Survival analysis showed a small trend in favour of 5FU + LV over 5FU + α-IFN, but this advantage was not statistically significant (overall HR = 1.11; 95% CI = 0.99–1.24; \( P = 0.066 \)) (Figure 4). Median survivals were 11.7 months for patients allocated to 5FU + LV and 11.3 months for patients allocated to 5FU + α-IFN. The survival difference reached statistical significance in the group of trials using the same 5FU schedules in both treatment arms (HR = 1.29; 95% CI 1.07–1.57; \( P = 0.008 \)). There was some heterogeneity in this group of trials, but which did not reach a statistically significant level (\( P = 0.67 \)).

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Individual patient data used for the two meta-analyses were combined to identify prognostic factors for response and survival (3254 patients). Sex, age, performance status (PS), primary tumour site, previous adjuvant chemotherapy, metastatic site, and allocated treatment (no α-IFN vs. α-IFN) were considered in these analyses. In a logistic regression model, metastases confined to the liver (\( P < 10^{-4} \)), and primary rectal tumours (\( P = 0.042 \)) were the independent favourable prognostic factors for tumour response. Tumour response rates were 26% for patients with metastases confined to the liver versus 20% for the others. Patients with rectal cancer had a 26% tumour response rate, vs. 22% with colon tumour.
In a Cox regression model, good PS (P = 0.042), medium tends to block the synergic effect (Neele and John, 1991). Interferon may also modify the plasma pharmacokinetics of 5FU (Lindley et al, 1990; Danhouser et al, 1991). Finally, 5FU may influence the immunomodulatory actions of interferon (Neele and John, 1991). However, despite more than 3000 patients included in randomized trials, the clinical impact of combining α-IFN to 5FU remained debatable.

The 2 meta-analyses presented here address the efficacy of α-IFN combined with 5FU in advanced colorectal cancer. Tumour response rate and survival were the two main end points. Toxicity was not studied, since at the time of beginning these meta-analyses individual trials had already demonstrated that the addition of α-IFN to a 5FU regimen led to an increased risk of neutropenia, mucositis, and neurotoxicity, and was associated with flu-like syndromes. α-IFN also produced a significant impairment of quality of life in the MRC trial (Seymour et al, 1996).

The meta-analysis of trials comparing 5FU ± LV to a similar 5FU regimen plus α-IFN failed to show any difference between control and experimental arms in terms of tumour response or survival. The tumour response rate with 5FU bolus alone reported in the group of trials comparing 5FU to 5FU + α-IFN was rather high (19%), compared to tumour responses reported for patients receiving 5FU bolus in the 4 meta-analyses previously performed by our group, which varied between 11% and 14% (ACCPM, 1992, 1994; MAGIC, 1996, 1998a). This may reflect a selection of patients with favourable prognostic characteristics in trials included in the present meta-analysis, but does not invalidate our finding of no difference between 5FU alone and 5FU + α-IFN. It should also be noted that the doses of 5FU delivered in the 5FU alone arms were generally high compared with the 5FU doses reported in our previous meta-analyses.

In contrast, the meta-analysis of trials comparing 5FU + LV to 5FU + α-IFN showed higher response rates and a trend towards longer survival in favour of 5FU + LV. In this set of trials, the overall tumour response rate and the median survival of patients receiving 5FU + LV (23% and 13 months, respectively) were remarkably similar to those reported previously in the meta-analysis of trials comparing 5FU to 5FU + LV (ACCPM, 1992), (23% and 11.5 months, respectively). Thus, the advantage of 5FU + LV over 5FU + α-IFN observed in the present meta-analysis does not seem to be due to some selection bias that might have favoured patients allocated to the 5FU + LV arm.

In this meta-analysis, the stratification of trials by type of 5FU administration (Figures 3 and 4) showed a statistically significant
advantage of 5FU/LV over 5FU+IFN in the group of trials using the same 5FU schedules in both arms. By contrast, there was no difference between the two treatment arms when 5FU was administered by bolus in the 5FU/LV arm and by continuous infusion in the 5FU + IFN. This could be linked to the tumour response and survival advantage of 5FU continuous infusion over 5FU bolus demonstrated in one of our previous meta-analyses (MAGIC, 1998a).

5FU dose intensity is not a valid parameter when comparing bolus versus infusion or mixed regimens. Consequently, no attempt was made to stratify trials according to 5FU dose intensity.

The prognostic factor analysis confirms well-established results, such as the key role of performance status for survival. Other findings are less classical, such as the role of primary and metastatic tumour sites, and are currently under investigation by our group, on the basis of 7000 individual patient data with advanced colorectal cancer. In the adjuvant setting, a trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP-C05) also failed to show any advantage for 5FU + LV + α-IFN over 5FU + LV in patients with stage II-III colon cancer (Wolmark et al, 1998). On-going studies are currently addressing the interest of other types of interferon, such as α-2c IFN and β-IFN (Villar Grimalt et al, 1999). However, new agents, such as CPT-11 (irinotecan) (Douillard et al, 2000; Saltz et al, 2000) or oxaliplatin (de Gramont et al, 2000) have demonstrated clinical benefits in advanced colorectal cancer, and are therefore more plausible candidates for the adjuvant setting.

We conclude that α-IFN does not increase the efficacy of 5FU in advanced colorectal cancer, and should not be offered in routine clinical practice.

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