Predictive factors of survival in patients with advanced colorectal cancer: an individual data analysis of 602 patients included in irinotecan phase III trials

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Background: The infusional LV5FU2 and Arbeitsgemeinschaft Internische Onkologie (AIO) regimens are used widely in the treatment of advanced colorectal cancer. Irinotecan combined with these regimens increases survival in front-line treatment. Irinotecan also improves survival in second-line treatment.

Patients and methods: Univariate and multivariate analyses based on the individual data of 602 patients included in two phase III trials were performed to determine predictive factors of survival in advanced colorectal cancer.

Results: Three factors were independently associated with a better progression-free survival: weight loss < 5% [hazard ratio (HR) 1.25; 95% confidence interval (CI) 1.00–1.58], World Health Organization performance status (WHO PS) 0–1 (HR 1.29; 95% CI 1.08–1.54) and irinotecan (CPT-11)-containing regimens (HR 1.48; 95% CI 1.03–2.13). Five factors were independently associated with a better overall survival: weight loss < 5% (HR 1.67; 95% CI 1.29–2.14), WHO PS 0–1 (HR 1.88; 95% CI 1.27–2.75), one or two metastatic sites (HR 1.24; 95% CI 1.01–1.53), alkaline phosphatase values not over twice the normal range (HR 1.71; 95% CI 1.30–2.24) and CPT-11-containing regimens (HR 1.31; 95% CI 1.07–1.61).

Conclusions: The present analysis confirms that CPT-11-based chemotherapy regimens are independently associated with a better survival in patients with advanced colorectal cancer. Age was not identified as a prognostic factor in this analysis.

Key words: chemotherapy, colorectal neoplasms, irinotecan, prognostic factors

Introduction

Initially used alone, and then in combination with folinic acid (FA), 5-fluorouracil (5-FU) has been the main chemotherapy drug for the treatment of advanced colorectal cancer (ACC) for the past 40 years. A meta-analysis including 1219 patients demonstrated that continuous 5-FU infusion is superior to bolus administration in terms of response rate and survival, with less toxicity [1]. In Europe, the most widely used continuous infusion regimens of 5-FU are the LV5FU2 regimen [2], the AIO (Arbeitsgemeinschaft Interniste Onkologie, German Cooperative Group for Oncology) regimen [3, 4] and the Spanish Cooperative Group For Gastrointestinal Tumor Therapy TTD regimen [5]. Compared with the Mayo Clinic regimen, the LV5FU2 regimen is less toxic and significantly increases tumor response rate and progression-free survival (PFS), with a modest increase in overall survival (OS) [2]. The AIO regimen also increased PFS compared with the Mayo Clinic regimen in one randomized trial [3, 6], whereas in another trial the TTD regimen did not significantly improved PFS and OS compared with the Mayo Clinic regimen [5]. Irinotecan (CPT-11) is used in combination with these regimens. Two randomized trials have demonstrated that the infusional 5-FU (LV5FU2 and AIO regimens) in combination with CPT-11 significantly increase PFS [7, 8], while a significant advantage in terms of OS has been demonstrated in one trial [7], compared with the same regimens without CPT-11 in front-line treatment of ACC. CPT-11 also improves survival in second-line treatment compared with best supportive care [9] or infusional 5-FU [10].

Studies evaluating prognostic factors of survival in ACC patients treated with a bolus 5-FU-based regimen [11] or with...
the irinotecan (CPT-11)-based IFL (CPT-11–5-FU–leucovorin) regimen [12] have recently been published, but there were no available data on prognostic factors of survival in patients treated with the LV5FU2 or AIO regimen, with or without CPT-11. We have therefore performed a pooled analysis of data from the two published randomized trials using infusion-based 5-FU regimens with or without CPT-11 [7, 10].

Patients and methods

Analyses were based on individual data of 602 patients treated in the V302 [10] and V303 [7] trials. The methodology and results of these trials have been published previously.

Trial V302 [10]

Trial V302 included 267 patients (256 treated) whose cancer had progressed after 5-FU-based treatment and who were randomized to either CPT-11 monotherapy or infusional 5-FU (AIO, LV5FU2 or Lockich regimens). Patient entry criteria included: age 18–75 years; histologically proven progressive metastatic adenocarcinoma of the colon or rectum; World Health Organization performance status (WHO PS) of ≤2; and adequate hematological, renal and hepatic functions. One hundred and twenty-seven patients were randomly allocated to CPT-11 350 mg/m² as a 90-min intravenous infusion once every 3 weeks (300 mg/m² in patients aged >70 years or with WHO PS 2). One hundred and twenty-nine patients treated with the Lockich regimen were not included in the present analysis, since this regimen was not used in the V303 trial.

Trial V303 [7]

Trial V303 included a total of 387 patients (385 treated) with ACC who were randomized to first-line treatment with infusional 5-FU (AIO or LV5FU2) with or without CPT-11. Patients had to meet the following criteria: age 18–75 years; histologically proven adenocarcinoma of the colon or rectum; WHO PS of ≤2; adequate hematological, renal and hepatic functions; and no previous chemotherapy other than adjuvant chemotherapy finished >6 months before randomization. For the ‘no CPT-11’ group (186 patients), the AIO and LV5FU2 regimens were the same as for the V302 trial. For the CPT-11 group (199 patients), the regimens were: once weekly CPT-11 80 mg/m² with fluorouracil 2300 mg/m² in a 24 h infusion, plus FA 500 mg/m² (AIO-CPT-11 regimen); or every 2 weeks, CPT-11 180 mg/m² on day 1 with 5-FU 400 mg/m² bolus and 600 mg/m² by 22 h infusion, plus FA 200 mg/m² on days 1 and 2 (LV5FU2-CPT-11 regimen).

Statistical analysis

PFS was calculated from the date of randomization to the date of progression (or date of death in patient without progression). OS was calculated from the date of randomization to the date of death. The survival function was estimated using the Kaplan–Meier method [13].

The first part of the analysis consisted of the univariate comparison of survival functions for factors that could potentially affect the survival time using the log rank test. Univariate analysis describes the survival with respect to the factor under investigation, but necessarily ignores the impact of any others. We therefore performed a multivariate survival analysis to compare prognostic factors of survival after adjustment for the impact of other factors [14]. Different potential predictive variables were evaluated in univariate analyses: age (< 65 versus 65–75 years), sex, weight loss (< 5% versus ≥ 5%), WHO PS (0–1 versus 2), treatment line (1 versus 2), number of metastatic sites (1–2 versus ≥3), liver metastases (yes versus no), lung metastases (yes versus no), peritoneal carcinomatosis (yes versus no), serum carcinoembryonic antigen (CEA) value (< 50 versus > 50 ng/ml), alkaline phosphatase value [≤ 2 × upper normal limit] versus > 2N×, lactate dehydrogenase (LDH) value (N versus > N), leukocyte count (< 10000/µl versus > 10000/µl), treatment line (1 versus 2) and CPT-11-containing regimen (yes versus no). A Cox proportional hazard regression, stratified on treatment line, was performed to estimate prognostic factors associated with survival in the multivariate analysis. The LDH value was only available for 503 patients and was excluded from the multivariate analysis. All other variables associated with survival in the univariate analysis at the 0.1 level were entered into the Cox model.

The calculations were performed using Stata statistical software (Stata Corporation, College Station, TX, USA).

Results

Patients

Six hundred and two patients were included in the analysis: 217 treated in V302 trial and 385 treated in V303 trial. There were 358 males and 244 females, with a median age of 50 years (range 24–75). Patient characteristics at the time of randomization are presented in Table 1.

Table 1. Patient characteristics at time of randomization and survival by trial and treatment

<table>
<thead>
<tr>
<th>n</th>
<th>Males</th>
<th>Age group, years</th>
<th>Weight loss &lt;5%</th>
<th>WHO PS 0–1</th>
<th>1–2 organs involved</th>
<th>PFS in months (95% CI)</th>
<th>OS in months (95% CI)</th>
</tr>
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<tbody>
<tr>
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<tr>
<td>Irinotecan group</td>
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<td>135</td>
<td>186</td>
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</tr>
<tr>
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<td>61</td>
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<tr>
<td>No irinotecan group</td>
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<td>61</td>
<td>29</td>
<td>81</td>
<td>87</td>
<td>74</td>
</tr>
</tbody>
</table>

WHO PS, World Health Organization performance status; PFS, progression-free survival; CI, confidence interval; OS, overall survival.
Predictive factors of PFS

Variables significantly associated with PFS in the univariate analysis were: weight loss, PS, number of metastatic sites, alkaline phosphatase, LDH, treatment line and CPT-11-containing regimens (Table 2). The comparisons for age and liver metastases only just reached the 0.05 significance level. Whereas patients with CEA > 50 ng/ml had the same median PFS as those with a lower CEA value, the log rank test was highly significant ($P = 0.01$) because the survival curve diverged after the fifth month.

Results of the multivariate analysis are presented in Table 3. Three factors were independently associated with a better PFS: weight loss < 5% [hazard ratio (HR) 1.25; 95% confidence interval (CI) 1.00–1.58; $P = 0.047$], WHO PS 0–1 (HR 1.29; 95% CI 1.08–1.54; $P = 0.005$) and CPT-11-containing regimens (HR 1.48; 95% CI 1.03–2.13; $P = 0.035$). Age was not associated with PFS.

Predictive factors of OS

Variables significantly associated with OS in the univariate analysis were: weight loss, PS, number of metastatic sites, peritoneal carcinomatosis, CEA value, alkaline phosphatase value, LDH value, treatment line and an CPT-11-containing regimen (Table 2).

Results of the multivariate analysis are presented Table 4. Five factors were independently associated with a better OS in multivariate analysis: weight loss < 5% (HR 1.67; 95% CI 1.29–2.14; $P < 0.001$), WHO PS 0–1 (HR 1.88; 95% CI 1.27–2.75; $P = 0.03$), two or less metastatic sites (HR 1.24; 95% CI 1.01–1.53; $P = 0.04$), alkaline phosphatase $\leq 2 \times N$ (HR 1.71; 95% CI 1.30–2.24; $P < 0.001$) and CPT-11-containing regimen (HR 1.31; 95% CI 1.07–1.61; $P = 0.009$). Age was not associated with OS.

Discussion

This pooled analysis based on the individual data of 602 patients treated either with CPT-11 monotherapy or an infusional 5-FU-based regimen with or without CPT-11 in two randomized trials confirms the prognostic role of previously identified factors such as PS and weight loss and add to the existing data on patients treated with CPT-11.

Köhne et al. [11] recently published a multivariate analysis of 3825 patients with 5-FU-based treatment for metastatic colorectal cancer. PS, number of metastatic sites, white blood cell count and alkaline phosphatase were the main clinical parameters associated with survival, and were correlated with three risk groups for patients: low, medium and high, with corresponding median survivals of 15, 10.7 and 6.1 months. The major prognostic significance of PS has previously been reported in several studies [9, 12, 15–17] and indeed, a good performance status (WHO 0–1) is associated with a better PFS or OS in our analysis. As also reported previously [9], weight loss > 5% was independently associated with a worse PFS and OS. The number of metastatic sites, CEA, alkaline phosphatase, LDH, and treatment line were not significant predictors of survival.
Factors associated with a better overall survival in multivariate analysis (Cox proportional hazard regression stratified on treatment line)

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
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<td>1.48</td>
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</table>

CI, confidence interval; WHO PS, World Health Organization performance status.

Factors associated with a better progression-free survival in multivariate analysis (Cox proportional hazard regression stratified on treatment line)

<table>
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<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
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phosphatase and LDH were significantly associated with PFS and OS in the univariate analysis. In the multivariate analysis, no tumor-related factors were associated with PFS, whereas the number of metastatic sites and alkaline phosphatase were significantly associated with OS, as previously reported [9, 11, 12, 18]. Despite a strong association with survival in the univariate analysis, LDH was not introduced in the multivariate analysis, since its value was not available for almost 20% of the patients and this may have distorted the regression results. A CPT-11-based regimen also independently predict for a better PFS and OS compared with 5-FU-based regimen, which was previously demonstrated in randomized trials [7, 8, 10, 19]. A CPT-11-based regimen seems to be the most important factor associated with PFS (HR 1.48 compared with 1.29 for PS and 1.25 for weight loss), but PS and weight loss remain the main prognostic factors for OS (HR 1.88 and 1.71, respectively, compared with 1.31 for CPT-11).

Age was not associated with survival, and patients between 65 and 75 years old had the same prognosis as younger patients. It was noted that multivariate analyses results were similar when 70 years was chosen as the cut-point for young and elderly patients. Age has rarely been reported as a prognostic factor of colorectal cancer survival in randomized trials [20], whereas epidemiological data clearly show that patients above the age of 75 years have a worse prognosis than younger patients [21, 22], mainly because they are less frequently actively treated. By design, most clinical trials in colorectal cancer have limited recruitment to generally fit patients <75 years old, and very few data on efficacy and tolerance of the current standard regimen are available for this population. This is problematic, since the incidence of colorectal cancer in the elderly is steadily increasing, with >40% of the cases occurring in patients aged 75 years and above [23]. A subgroup analysis performed among patients treated with the LV5FU2–CPT-11 regimen in the V303 trial demonstrated that there was no difference in tumoral response rate or PFS and OS rates for patients aged between 65 and 75 or younger patients [24], but more data in patients older than 75 years is needed to confirm treatment recommendations. To resolve this issue, randomized clinical trials focusing on elderly patients are awaited, and indeed, the Fédération Francophone de Cancérologie Digestive is conducting a study comparing treatment by LV5FU2 or simplified LV5FU2 with the same regimen with CPT-11 (LV5FU2-CPT-11 and FOLFIRI regimens) in the first-line treatment of ACC in patients aged 75 years and above. Trials such as this one will enable us to confirm whether the prognostic factors identified in this analysis for patients under 75 years old hold true for those over 75.

References


