Prognostic factors for 60-day mortality in first-line treatment of metastatic colorectal cancer (mCRC): individual patient analysis of four randomised, controlled trials by the AIO colorectal cancer study group

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Background: The 60 day mortality is an established parameter for chemotherapy-related safety in randomised trials for metastatic colorectal cancer (mCRC). Prognostic factors associated with 60-day mortality would be helpful to identify high-risk patients in advance.

Patients and methods: Individual baseline patient data from four randomised, controlled trials from the Arbeitsgemeinschaft Internistische Onkologie (AIO) study group were retrospectively analysed. Chemotherapy consisted of fluoropyrimidine (5-FU/capecitabine), irinotecan, oxaliplatin with or without bevacizumab or cetuximab. Prognostic factors were identified by univariate and multivariate logistic regression models in two cohorts: one limited to ECOG PS 0 and 1 and one including ECOG PS 2 patients.

Results: A total of 1377 patients were evaluated. The analysis of ECOG PS 0, 1 and 2 patients consisted of 898 patients where a total of 33 deaths within the first 60 days of treatment (3.7%) occurred. In multivariate analysis, 60-day mortality was significantly associated with ECOG PS 2 and high leucocyte count (white blood cell, WBC). Odds ratio was 6.28 for WBC and 12.92 for ECOG PS 2. Exclusion of ECOG PS 2 patients but inclusion of one trial limited to ECOG PS 0 and 1 patients resulted in 1302 assessable patients and 44 early deaths (3.4%). In both cohorts, around 50% of deaths were disease related. WBC was confirmed as a significant risk factor for early death (OR 7.60). A combined score using ECOG PS 2 and WBC ≥8.000/µl is able to identify high-risk patients with a sensitivity of 18% and specificity of 98%.

Conclusions: In this large retrospective analysis of individual patient data, around 50% of early deaths were disease related. Elevated WBC was found strongly associated with increased 60-day mortality in first-line treatment of mCRC. The proposed AIO-60-Day-Mortality score serves as an additional trial exclusion criterion.

Key words: 60-day mortality, prognostic factors, metastatic colorectal cancer, first-line chemotherapy, randomised trials

Introduction

The reported 60-day mortality in clinical trials for chemotherapy treatment of metastatic colorectal cancer (mCRC) is a hallmark of chemotherapy-related safety. However, while the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines has strictly defined serious adverse events in clinical trials, early mortality in clinical trials is only loosely defined. In mCRC, the 60-day mortality rate, specified as death within first 60 days of chemotherapy treatment is widely used, but not claimed in standardised reporting of clinical trial data [1]. In addition, the differentiation between treatment-related and disease related death is still uncommon. Current clinical trials using combination chemotherapy regimens with or without monoclonal antibodies report all-cause mortality rates between 2% and 4% [2-4].

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In 2002, Koehne et al. proposed three risk groups as clinical determinants of long-term survival using four baseline parameters: performance status, white blood cell count (WBC), alkaline phosphatase (AP) and number of metastatic sites [5].

Based on established prognostic factors for long-term survival in chemotherapy treatment of mCRC, we recently identified WBC and lactate dehydrogenase (LDH) as prognostic factors for all-cause 60-day mortality in an irinotecan-based trial [6]. In contrast, Díaz et al. investigated prognostic factors proposed by Koehne et al. in patients treated with combination chemotherapy and were not able to find a relationship between baseline laboratory characteristics and severe toxicity [7].

In the present study, individual data from four randomised first-line trials for treatment of mCRC from the Arbeitsgemeinschaft Internistische Onkologie (AIO) were analysed to define prognostic factors for early mortality in ECOG PS 0, 1 and 2 patients and to propose a scoring system that could serve as inclusion criterion for randomised, controlled trials [8–11].

material and methods

We carried out a retrospective analysis of individual patient data from four randomised first-line trials for treatment of mCRC from the AIO: first, a total of 474 patients were enrolled in a phase III study to receive either capcitabine plus oxaliplatin (CAPOX) or fluorouracil and leucovorin plus oxaliplatin (FUFOX) for first-line treatment of mCRC [9]. Secondly, the AIO KRK 0104 randomised phase II trial compared cetuximab plus capcitabine and irinotecan (CAPRI) with cetuximab plus capcitabine and oxaliplatin (CAPOX) as first-line treatment in 177 patients with mCRC [8]. Furthermore, the AIO KRK 0604 randomised phase II trial enrolled 247 patients to receive either capcitabine plus irinotecan (CAPRI) or capcitabine plus oxaliplatin (CAPOX) in combination with bevacizumab [10]. The FIRE-1 phase III trial compared chemotherapy with either FU/FIRI or mIROX in 479 patients with mCRC [11].

All trials were carried out according to the Declaration of Helsinki and Good Clinical Practice Guidelines and in accordance with the AIO at multiple treatment sites in Germany between July 2000 and December 2006. Trial protocols were approved by local ethics committee at each participating site. Written informed consent was obtained from all patients before study participation.

Trial inclusion and exclusion criteria are listed in the supplementary material S1, available at Annals of Oncology online.

evaluation of 60-day mortality

The 60-day mortality was defined as death within the first 60 days of chemotherapy treatment. Baseline characteristics of all participating patients summarised in supplementary material S3 and S4, available at Annals of Oncology online were analysed.

To investigate causes of death, trial database, SAE report and/or anonymised medical records were evaluated by four investigators (CG, DPM, CS and VH). Causes of death were classified as follows: disease-related (death related to tumour progression), sepsis, severe gastrointestinal toxicity, thromboembolic events, cardiac and bleeding events.

statistical considerations

Fisher’s exact test and χ² test were applied to compare patient characteristics. Prognostic factors were identified by univariate and multivariate logistic regression models. In particular, a backward elimination algorithm was used to select significant covariates from all available patient baseline characteristics. The significance level for selecting these covariates was set at 0.157 which is about equivalent to Akaike’s information criterion (AIC). Simultaneously, a check for nonlinear relationships of continuous covariates with the dependent variable was carried out by relying on fractional polynomials. Additionally, the discriminatory performance of the multivariate logistic regression model was evaluated by calculating the receiver operating characteristic (ROC) curve and the corresponding area under the curve (AUC).

All P-values were calculated as two-sided, and $P < 0.05$ was considered as statistically significant. All statistical analyses were conducted using the R version 2.13.2 statistical package (R Development Core Team Vienna, 178 Austria, 2012. Available from: http://www.r-project.org).

results

Due to different inclusion criteria with regard to performance status, we carried out two different analyses: At first, risk factors were investigated in ECOG PS 0, 1 and 2 patients from three AIO trials: the AIO 0104 trial, the AIO 0604 trial and the CAPOX/FUFOX trial. Individual patient data from 898 patients were available for analysis. (supplementary material S2, available at Annals of Oncology online) Among the 898 patients, a total of 33 deaths occurred within the first 60 days of chemotherapy treatment (60-day mortality rate 3.7%). Patient baseline characteristics are summarised in supplementary material S3, available at Annals of Oncology online.

Second, the analysis was also carried out in the subgroup of ECOG PS 0 and 1 patients including the FIRE-1 trial ($n = 479$), where Karnofsky performance status (KPS) was required ≥70% (i.e. ECOG PS 2 was excluded) per protocol. Accordingly, for analysis in ECOG 0 and 1 patients, a total of 1302 patients are assessable and with a 60-day mortality rate of 3.4% (44 of 1302). Patient baseline characteristics are summarised in supplementary material S4, available at Annals of Oncology online.

patient population

The median age of the 33 patients who died within the first 60 days was slightly older (66 versus 64 years) than the median patient population. When compared with patients alive after 60 days, the proportion of patients with ECOG 2 was significantly greater (39% versus 4%; $P < 0.001$) in patients who died within the first 60 days. ECOG 1 was comparable with 33% and 38%, respectively. ECOG 0 was less frequent in patients of the 60-day mortality group (27% versus 54%, $P < 0.001$). Localisation of metastases was comparable between the two groups. With regard to number of metastatic sites an imbalance was present with 28% missing data in patients alive after 60 days. Also CEA levels were not reported in 52% of patients in the 60-day mortality group and 32% of patients alive after 60 days. Baseline WBC was significantly higher in patients who died within 60 days (67 versus 43%; $P = 0.007$), while LDH levels, AP were comparable (supplementary material S3, available at Annals of Oncology online).

In the group of ECOG PS 0 and 1, patients who died within 60 days were also older (median 66.0 versus 63.6 years) than the
median patient population. Compared with patients alive, the proportion of ECOG 0 was significantly lower (43% versus 63%; P = 0.010) in patients who died within 60 days. Again, with regard to number of metastatic sites an imbalance was present with 20% missing data in patients alive after 60 days while localisation of metastases was comparable between the two groups. CEA levels were not reported in 36% of patients in the 60-day mortality group and 25% of patients alive after 60 days. The proportion of patients with a WBC ≥8.000/μl was significantly greater in patients with early death (66% versus 42%; P = 0.006). Levels of LDH and AP were comparable between patients with early death and patients alive after 60 days (supplementary material S4, available at "Annals of Oncology online").

all-cause 60-day mortality

The main cause of death within the first 60 days of treatment was classified as disease-related (18 of 33; 54.5%). Death related to sepsis occurred in four patients (12.1%), while severe gastrointestinal toxicity lead to two deaths (one small bowel ileus, one GI-syndrome with diarrhoea, vomiting and dehydration) [12]. Two deaths were related to thromboembolic events (one pulmonary embolism, one arterial thromboembolic) and two deaths were related to cardiac events (one cardiac arrhythmia and one cardiac de-compensation), whereas all four deaths were not related to bevacizumab. One bleeding event (duodenal bleeding) occurred in a trial without deficiency in a patient with a history of chronic obstructive pulmonary disease. In three patients, the exact cause of death remains unclear.

Within the 44 patients in the ECOG PS 0 and 1 group, disease-related early deaths were also the main cause of death (21 of 44; 47.7%) (supplementary material S5, available at "Annals of Oncology online").

risk factors for 60-day mortality in ECOG PS 0, 1 and 2 patients

In multivariate analysis of all available baseline patient data from 898 patients with ECOG PS 0, 1 and 2 summarised in Table 1, only elevated WBC and ECOG PS 2 were found to be associated with an increased risk of death within the first 60 days of treatment. Odds ratio for WBC was 6.28 [95% confidence interval (CI) 2.17–19.06; P < 0.001]. For ECOG PS 1 versus ECOG PS 0, Odds ratio was 1.61 (95% CI 0.64–4.24; P = 0.310) and for ECOG PS 2 versus ECOG PS 0, Odds ratio was 12.92 (95% CI 4.73–36.52; P < 0.001). Other tumour and patient baseline characteristics (primary tumour site, adjuvant pre-treatment, development of metastasis, T- and N-stage, No. of metastatic sites and localisation of metastases, CEA, AP and treatment regimen) were not found to be associated with early mortality (Table 1).

According to the stratification criteria that were used in all four randomised trials, the cut-off for WBC was set at ≥8.000/μl. The ROC analysis was then carried out an obtained an AUC of 0.75 (95% CI 0.64–0.87). Sensitivity was 71% and specificity was 58% (supplementary material S6, available at "Annals of Oncology online").

Table 1. Multivariate analysis (ECOG PS 0, 1 and 2)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>0.61</td>
<td>0.12–3.08</td>
<td>0.551</td>
</tr>
<tr>
<td>Age</td>
<td>1.13</td>
<td>1.02–1.255</td>
<td>0.310</td>
</tr>
<tr>
<td>ECOG PS 1 versus ECOG PS 0</td>
<td>1.61</td>
<td>0.64–4.24</td>
<td>0.314</td>
</tr>
<tr>
<td>ECOG PS 2 versus ECOG PS 0</td>
<td>12.92</td>
<td>4.73–36.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary tumour site</td>
<td>0.41</td>
<td>0.07–2.28</td>
<td>0.306</td>
</tr>
<tr>
<td>Adjuvant pretreatment</td>
<td>3.89</td>
<td>0.38–20.20</td>
<td>0.255</td>
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<tr>
<td>Development of metastasis</td>
<td>0.44</td>
<td>0.04–4.40</td>
<td>0.483</td>
</tr>
<tr>
<td>T-stage</td>
<td>0.82</td>
<td>0.21–3.25</td>
<td>0.777</td>
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<tr>
<td>N-stage</td>
<td>0.89</td>
<td>0.34–2.36</td>
<td>0.814</td>
</tr>
<tr>
<td>No. of metastatic sites</td>
<td>1.27</td>
<td>0.92–1.76</td>
<td>0.151</td>
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<td>LDH</td>
<td>1.00</td>
<td>1.00–1.01</td>
<td>0.991</td>
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<tr>
<td>CEA</td>
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<tr>
<td>AP</td>
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<td>1.00–1.01</td>
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<tr>
<td>WBC</td>
<td>6.28</td>
<td>2.17–19.06</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; WBC, white blood cell count; OR, odds ratio; CI, confidence interval.

risk factors for 60-day mortality in ECOG PS 0 and 1 patients

Individual patient baseline data from 1,302 patients were included in the multivariate analysis of ECOG 0 and 1 patients. Elevated WBC was found to be associated with an increased risk of death within the first 60 days of treatment. Odds ratio for WBC was 7.60 (95% CI 3.11–18.60; P < 0.001). Again, other tumour and patient baseline characteristics did not increase the risk of early mortality (supplementary material S7, available at "Annals of Oncology online").

AIO-60-day-mortality score

To define a score that can be used in daily clinical routine for the reduction of early all-cause mortality, the two significant parameters obtained in the multivariate analysis have been applied. At first, WBC < 8.000/μl does not count for the AIO-60-Day-Mortality Score, while ≥8.000/μl scores one point. Secondly, an ECOG PS of 0–1 does not count while ECOG PS 2 scores one point. Odds ratio for AIO-60-Day-Mortality Score 1 was 2.51 (95% CI 1.00–6.28; P = 0.050). For AIO-60-Day-Mortality Score 2, the odds ratio was 30.54 (10.58–88.20; P < 0.001).

The calculated sensitivity for this combined score was 18% and specificity was 98%. The positive predictive value was 32% while the negative predictive value was 97%. Estimation of the positive likelihood ratio (LR) resulted in 9 and the negative LR was 0.84. The proposition of the AIO-60-Day-Mortality Score is summarised in Table 2.

discussion

Numerous analyses have been carried out to evaluate baseline characteristics as prognostic factors for patient outcome [5, 13–16]. Relating to this, elevated WBC, as well as the absolute neutrophil count and neutrophil lymphocyte ratio were associated with poor survival in mCRC [15, 17, 18].
A pooled analysis of nine clinical trials investigated the role of ECOG PS with regard to treatment efficacy and toxicity [16]. While ECOG PS 2 patients obtained similar treatment benefit as patients with ECOG PS 0–1, an increased risk of toxicities could be observed at the same time. This resulted in a significantly increased 60-day all-cause mortality rate of 12.0% compared with only 2.8% among ECOG PS 0–1 patients.

To the best of our knowledge, the present analysis of four randomised first-line trials is the largest individual patient analysis with focus on early mortality in mCRC. Nowadays, ECOG PS 2 patients are widely excluded form clinical trials. To assess risk factors for early death in this setting, the analysis was carried out also in ECOG PS 0–1 patients, where one additional trial (FIRE-1 trial) could be included [11]. In summary, we were able to confirm previous findings of elevated WBC being associated with an increased risk of death within the first 60 days of chemotherapy treatment in ECOG PS 0, 1 and 2 patients [6]. While in our previous analysis KPS only showed a trend towards an increased risk of early mortality, the present analysis of 898 patients found ECOG PS 2 being strongly associated with early death. In contrast to previous findings, in the present analysis LDH levels were not found to be significantly associated with 60-day mortality. Similar to the analysis carried out by Sargent et al., approximately half of early deaths in the evaluated trials were caused by disease progression [16]. Notwithstanding that ECOG PS 2 can be prognostic per se, based on the available data it is not possible to differentiate ECOG PS 2 patients being specifically at risk by cancer-related symptoms due to rapid tumour progression or relevant pre-existing comorbidities.

The proposed AIO-60-Day-Mortality Score may be used as a simple supplementary tool before trial enrolment in order to reduce early all-cause mortality in clinical trials by excluding high-risk patients with ECOG PS 2 with an increased WBC of ≥8,000/μl. It is important to note, that ECOG PS 2 patients are not intended to be generally excluded, as this is current practice in various phase II and III trials. To the contrary, trial accrual would not be particularly affected by the hypothesised post-hoc adoption of the AIO-60-Day-Mortality Score: only 4.0% of patients among the three trials reflecting 36 patients would not have been enrolled. On the other hand, the application of the AIO-60-Day-Mortality Score to the present data would have prevented ten early deaths within the trials, lowering the all-cause mortality rate to 2.6%. In this regard, the combination of ECOG PS 2 together with WBC as a cut-off variable was chosen to detect patients at risk for all-cause mortality without delaying trial accrual at the same time. We therefore decided to design the score with focus on specificity and to accept a certain loss with regard to sensitivity.

There are several limitations given in the present study: At first, the four AIO trials were retrospectively analysed and consequently, our findings are only suggestive and need to be confirmed in further analyses. However, with regard to baseline characteristics and the time frame of trial conduction, the four trials are comparable in principle and the fact of ECOG PS 2 patients being excluded in the FIRE-1 trial has been taken into account by performing two separate analyses. Secondly, baseline measures for CEA were missing in nearly one third of patients. Accordingly, its prognostic value in not fully explored in the present analysis. In addition, it can be also criticised that patients with disease-related early mortality have been enrolled despite the inclusion criterion ‘life expectancy >3 months’. As physicians generally tend to overestimate the prognosis of individual patients, the use of scoring systems has been shown to improve the accuracy of survival expectations [19]. Relating to this, our proposed score may add certain value to the physicians’ decision-making.

In conclusion, with the adoption of the AIO-60-Day-Mortality Score, the 60-day all-cause mortality may be reduced in further clinical trials without compromising trial accrual. The AIO-60-Day-Mortality Score can be used to identify high-risk patients that may not be optimal candidates for clinical trials and that may receive chemotherapy with intensified surveillance and treatment escalation strategies outside of clinical trials.

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**Disclosure**

CG: Travel support: Roche. UG: Honoraria: Merck, Roche, Sanofi-Aventis, Amgen, Hexal, Falk; Advisory Board: Merck, Roche, Sanofi-Aventis, Amgen, Lilly, Bayer. RPL: Honoraria, travel support and a research grant: Merck. WS: honoria and advisory board member: Roche, Merck, Astra Zeneca, Amgen and Apicent. AR-S: honoria: Amgen, Roche, Pfizer, Sanofi-Aventis, Merck; Advisory board member: Amgen, Roche, Pfizer, Sanofi-Aventis, Merck; Studies sponsored by: Roche, Sanofi-

<table>
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<tr>
<th>AIO-60-Day-Mortality Score</th>
<th>WBC</th>
<th>ECOG PS</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;8.000/μl</td>
<td>0 or 1</td>
<td>1.00</td>
<td>30.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>≥8.000/μl</td>
<td>0 or 1</td>
<td>2.51</td>
<td>10.58</td>
<td>&lt;0.001</td>
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<tr>
<td>2</td>
<td>≥8.000/μl</td>
<td>2</td>
<td>30.54</td>
<td>10.58</td>
<td>&lt;8.000</td>
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</table>

WBC, white blood cell count; ECOG PS, ECOG Performance Status, OR, odds ratio; CI, confidence interval.
Aventis, Celgene. SS: Honoraria: Merck, Roche, Amgen and Sanofi-Aventis; Advisory board: Merck, Roche, Bristol Meyer Squibb; Travel support: Roche and Merck. VH: Travel support and honoraria: Roche, Merck and Sanofi-Aventis. Research support: Roche, Merck and Sanofi-Aventis. All remaining authors have declared no conflicts of interest.

Trial Registration: not available

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