Clinical predictive factors

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Introduction

Over the last ten years we have witnessed a meaningful change in the treatment options of patients with metastatic colorectal cancer. However, not only does the composition of chemotherapy regimens, integrating the three anti-neoplastic agents fluoropyrimidines, irinotecan and oxaliplatin and the antibodies directed against the epidermal growth factor-receptor (EGFR) or vascular endothelial growth factor (VEGF), have to be considered, but the concepts of chemotherapy, aiming for cure in case of potential secondary resection of metastases or aiming for palliation, also provide challenges. Therefore, it does not come as any surprise that clinicians experience difficulties in defining a standard of care for their patients.

The problem

One of the points of discussion is whether upfront combination chemotherapy or the sequential use of drugs and regimens in the continuum of care of patients should be used [1]. Randomised trials [2,3] that have tried to address these questions, including more than 3000 patients, have been criticised because their low median survival of not more than 17 months was found to be inappropriate when compared to other randomised studies. Of concern is that patients starting with monotherapy would be deprived of follow-up treatment options due to a potential deterioration of performance status (PS) following insufficient fluoropyrimidine monotherapy. The current dogma calls for the use of all three cytotoxic agents based on a positive correlation found with the number of drugs available in studies and the median overall survival observed in those studies [4]. At ASCO 1998, when only 5-fluorouracil was available for any line of treatment, we presented data from 386 patients with a median survival of 12 months, which was acceptable at that time. The survival of 182 patients (47% of all patients) who received 5-FU as a second line treatment was 19 months and for those 80 patients (21% of all patients and 44% of the 2nd line cohort) who received 5-FU as third line treatment, survival was already 24 months. A total of 44 patients (11% of all patients and 55% of the 3rd line group) even received 4th line 5-FU and survived 27 months. Also, it was reported that the continuation of bevacizumab after progression of disease during first-line treatment into second- or even third-line would significantly increase long-term survival as compared to patients in whom bevacizumab was not continued [5]. However, all these reports may have been biased by unidentified patient characteristics or prognostic factors that might have compromised outcome independent of therapy:

(1) Patients entering studies on sequential therapy who had a low median survival were most likely representatives of a subgroup of patients without a chance of a secondary resection after response to combination chemotherapy, i.e. patients with a palliative option only.
(2) The finding that the number of drugs administered correlates to survival may have been biased by the fact that those patients who received all three drugs were those who had a more favourable tumour biology.
(3) The same could apply to patients who received bevacizumab beyond progression, a view that is supported by the observation that also patients receiving ondansetron beyond progression live longer [6].
(4) No biologics (bevacizumab or cetuximab) were used in either of the randomised trials comparing upfront combination chemotherapy versus sequential use of cytotoxics [2,3].

Thus, it will be important to define clinical, biological and molecular prognostic factors to better understand the cohort of patients under investigation and to better compare between different clinical studies. Indeed, clinical trials, while using similar patient selection criteria, often display a surprising variety in survival rates with similar chemotherapy regimens, and differences in patient characteristics or

prognostic factors are possible explanations. In order to avoid an imbalance of prognostic factors within treatment arms, patients entering randomised trials are usually stratified according to their PS. However, in addition, other prognostic factors or their constellation may impact survival of patients to a greater extent than any promising anti-neoplastic agent or drug combination.

The identification of independent prognostic factors may have important implications for routine clinical practice including a helpful guide for treatment decision making. From a clinical research perspective, the identification of prognostic factors for survival is important so as to have better stratified patients entered into randomised trials and also to help in the interpretation of data coming from non-randomised trials or retrospective hypothesis-generating studies.

Based on current available data it has been suggested to distinguish those patients who should receive upfront combination chemotherapy, because we need a tumour response that will later facilitate a curative operation of metastases, from those patients in which treatment is truly palliative only. The latter group constitutes the largest group of patients and here it would be especially helpful to estimate in advance whether a sequential approach of low toxic treatments is sufficient or whether combination chemotherapy should be used to prevent rapid tumour progression.

"Old fashioned" performance status

Clinicians often rely on their clinical judgement in these situations and, indeed, 70 years ago, Karnofsky and Burchenal [7] described a method of quantifying the functional status of cancer patients, now widely known and accepted as the Karnofsky PS (KPS), which is not only used in oncology but in all other fields of medicine as well. A similar tool, the Eastern Cooperative Oncology Group (ECOG) scale has been shown to highly correlate with the KPS and has gained increasing popularity, probably due to the fact that only a five-grade scale system is applied instead of a ten-grade scale system [8]. The Karnofsky scale has been validated as a global indicator of the functional status of patients with cancer after its reliability and validity had been assumed earlier without formal investigation [9]. Later, the validity between physicians and other health personnel was documented and its significance for predicting the prognosis of cancer patients is well documented in several studies. More recently, patient self-determined KPS and physician-determined KPS, along with other factors, were studied. Although the patient and physician ratings differed to some degree, the PS determined by the physician remained an important tool in daily clinical practice as well as in clinical trials [10]. Other investigators found that in those cases where the patient and the physician disagreed on the PS, the survival was worse [11]. Also, when including other parameters, three major groups of variables became apparent providing strong prognostic information including the physician's assessment of PS, the patient's self-assessment of PS and nutritional factors such as appetite, calorie intake and overall food intake [12]. In our daily practice, it is therefore sound routine to ask the patient about his or her wellbeing, their appetite and weight loss, and also to assess the patient's PS.

Gender and ethnicity

More recently, other factors determining the prognosis of patients with metastatic disease have been reported. In a large investigation screening nearly 57,000 patients with metastatic colorectal cancer, sex, age and ethnicity were associated with survival [13]. Of note, younger women aged 18–45 years lived longer than men of the same age group (17 months versus 14 months; $P < 0.0001$). However, in contrast, older women (75 years and older) had a significantly worse overall survival than older men ($P < 0.0001$). In a multivariate analysis, age, ethnicity and gender were associated with survival, and Hispanics followed by Caucasians, Asians, Africans, Americans and Native Americans, had the longest survival.

According to several investigations, gender appears to be a strong prognostic indicator for the tolerance of fluoropyrimidine-based treatment [14]. Also, regional differences in tolerability profiles of fluoropyrimidines have been described and more grade III–IV adverse events or dose reductions were reported in US versus non-US patients. When non-US patients were further divided into East Asia and the rest of the world, East Asian patients had the lowest and US patients the highest relative risk for toxicity or dose reductions. Thus, ethnicity may become a major player, especially in large multinational, randomised studies.

Sloan and colleagues [15] observed a greater toxicity in women following fluorouracil-based chemotherapy for colorectal cancer who had entered the North Central Cancer Treatment Group (NCCTG) trials. A total of 1093 women and 1353 men entered 12 different treatment arms. These toxicity differences were observed for gastrointestinal toxicity (stomatitis

and diarrhoea) but also for leucopenia and alopecia. This observation was confirmed by Australian and British investigators [16] in 439 patients treated with raltitrexed or 5-FU and leucovorin. Investigators from the South-West Oncology Group [17] reported on 1074 patients included in four trials and confirmed that toxicity was more extensive in women than in men treated with 5-FU. Pharmacokinetic and demographic markers of 5-FU toxicity were analysed in 181 patients treated with adjuvant 5-FU [18]. Gusella and colleagues reported that 5-FU area under the curve (AUC) was the best predictor for gastrointestinal toxicity with different levels in men and women. They also proposed different 5-FU doses to be used in women and men in order to achieve a similar AUC. Gamelin and colleagues [19] have taken these data to randomise patients according to a fixed dosing schedule or to a 5-FU dose adjustment regimen to achieve an AUC_{0-8} of 22–25 $mg \cdot h \cdot l^{-1}$. Not only could they demonstrate a wide range of 5-FU doses according to pharmacologically guided dosing, but there was also an indication of better survival for patients receiving the AUC-guided dose. Thus, while the determination of 5-FU pharmacokinetics is difficult, 5-FU dosing according to gender may be worth studying in the future.

TNM staging and prognosis in metastatic disease

We usually use the TNM staging system to decide on adjuvant chemotherapy after resection of the primary tumour and believe that at the time of metastases patients of all initial stages would behave similarly. Data from the adjuvant colon cancer endpoints (ACCENT) trial [20] taught us that patients with initial stage II disease had a better overall survival once metastases occurred than patients who formerly had stage III disease (18.2 months versus 12.5 months; hazard ratio [HR] 0.70; $P < 0.0001$). In addition, a significant interaction was found for survival between the patient's initial stage and time from randomisation to recurrence ($P = 0.00011$). This was especially true for patients with initial stage III disease but not in patients with initial stage II disease. Patients initially randomised to surgery alone had a superior survival following recurrence compared to those patients initially treated with 5-FU adjuvant chemotherapy (median 14.2 months versus 11.5 months; HR 0.83; $P = 0.0005$). Also, patients who were above $\geqslant 70$ years of age at the time of disease recurrence had a poorer survival than patients younger than 50 years (12.3 months versus 14.3 months; $P < 0.0001$). In a multivariate model, time to recurrence, initial stage, era of treatment and the initial application of adjuvant treatment all remained in the analysis. When the multivariate hazard ratios were examined by stage, each of the factors remained significantly associated with survival for patients with initial stage III tumours; however, time from randomisation to recurrence was not significantly associated with survival in stage II patients.

These data indicate that:

(1) Initial stage II and stage III disease are actually different diseases, and
(2) recurrence after adjuvant chemotherapy discriminates a group of patients with a worse tumour biology.

Peritoneal carcinomatosis

Peritoneal carcinomatosis is probably often not diagnosed but was reported to occur in about 12% of patients entering randomised studies [21]. Surely, patients with peritoneal carcinomatosis often have other sites of disease and for this reason they also represent an unfavourable subgroup of patients. Interestingly, we found among 3825 patients that infusional 5-FU resulted in a better survival than bolus 5-FU in patients without peritoneal carcinomatosis only (with peritoneal carcinomatosis: 10.8 months versus 14.6 months; $P < 0.0001$; without peritoneal carcinomatosis: 7.8 months versus 6.9 months; $P = 0.44$). However, when irinotecan combination chemotherapy was used, both patient groups with or without peritoneal carcinomatosis did benefit from irinotecan treatment.

Multivariate analyses

It is easy to prolong the list of prognostic factors especially if the cohort is large enough to identify even small, but statistically significant, differences in survival. Therefore, multivariate analyses including large numbers of patients with relevant prognostic factors better define the robustness of a single parameter. Several attempts have been undertaken to define clinical prognostic factors in various studies, however, seldom including more than 400 patients. In all of these studies, PS, either by the ECOG scale or by the Karnofsky scale, was found to be an independent prognostic factor. Other parameters were initial tumour stage, weight loss, age at diagnosis of metastases, site of metastases, level of carcinoembryonic antigen (CEA), level of haemoglobin and others. We managed to collect original data from studies, mainly published during the 1990s, using fluoropyrimidine either alone

or in combination with a drug that modulates the intracellular metabolism and metabolism of 5-FU (e.g. leucovorin, methotrexate, interferon, PALA) [22]. This large data set was split into a learning ($n = 2549$) and a validation set ($n = 1276$). Several laboratory parameters such as white blood cell count, platelets, haemoglobin, lactate dehydrogenase (LDH), alkaline phosphatase, transaminases, bilirubin, serum-protein and serum-albumin, and CEA were included in the analysis along with tumour-related parameters such as localisation of the primary tumour (colon or rectum), number of metastatic sites and whether lung, liver, lymph nodes or peritoneal metastases were present or not, together with a histological grading of the primary tumour. Other clinical parameters included age, ECOG PS, presence or absence of symptoms, weight loss and the use of prior adjuvant chemotherapy.

The parameters that remained in the multivariate analysis were ECOG PS, level of white blood cell count, number of involved tumour sites, alkaline phosphatase, haemoglobin, platelets, presence or absence of peritoneal carcinomatosis and whether the primary tumour was colon or rectum in origin. In order to simplify the model, four clinical parameters, ECOG PS 0.1 versus >1, white blood cell counts below or above 10×10^9/l, number of tumour sites 1 versus >1 and level of alkaline phosphatase above or under 300 U/l, could discriminate a low-risk group with a medium survival of 15 months, an intermediate-risk group with a medium survival of 11 months and a poor-risk group with a medium survival of about 6 months. The validation set of patients to samples confirmed the validity of this model.

This model has been used by our group [23] to test for other potential important parameters. Using data from a randomised trial of bolus versus infusional 5-FU, patients' self-reported health-related quality of life parameters, although seldom used in clinical routine, may have an additional prognostic value, adding to those parameters described above. The model of clinical parameters was also confirmed in colorectal cancer patients treated with chronotherapy [24].

It is obvious that only those clinical parameters that entered a multivariate analysis have a chance to appear as being independent. It is therefore possible that other potential parameters or constellations of variables may better describe and separate the prognosis of patients with metastatic colorectal cancer. Nevertheless, a learning and a validation sample clearly identifies these separate three risk groups. Whether other variables may add any information to this model remains speculative and probably unimportant as this tool not only confirms the results of other investigations but also discriminates between three risk groups.

The robustness or general applicability of such a model was proven by other investigators in cohorts of patients treated with combination chemotherapy including irinotecan and oxaliplatin. Recently, data from the intergroup study N9741 ($n = 1691$) were analysed using our low-, intermediate- and poor-risk criteria [25]. Study N9741 investigated the use of IFL (irinotecan, 5-FU (bolus), leucovorin), IROX (irinotecan, oxaliplatin) or FOLFOX (5-FU, leucovorin, oxaliplatin) in previously untreated patients with metastatic colorectal cancer. Interestingly, the three risk groups were confirmed discriminating a cohort of patients surviving 20.8 months, 17.4 months and 9.4 months ($P < 0.001$). Investigators from Spain [26] used our model in patients ($n = 142$) receiving either irinotecan- or oxaliplatin-based combination chemotherapy. The good risk group of patients survived a median of 20 months, the intermediate group 15.7 months and the poor risk group 6.8 months. Thus, these two studies confirmed the prognostic model in patients receiving combination chemotherapy.

Implications of the model

The implications of our model may be twofold.

Firstly, these prognostic parameters should be reported within the patient characteristics of phase II and phase III trials or these data should be used as stratification parameters to avoid imbalance of patients with good, intermediate or poor prognosis within treatment groups. In addition, the initial stage of the disease along with the use of adjuvant treatment will be informative. Although the use of prior adjuvant treatment was included in our model, the percentage of patients who actually received it was rather low in the time span covered by the studies included. It would be interesting to know whether both initial stage and the use of adjuvant treatment remain independent prognostic parameters within our model. Based on the prognostic factor model, Sorby and colleagues [27] have suggested a proposal for standardisation of patient characteristics, reporting and stratification.

Secondly, the model could help the clinicians to make treatment decisions with respect to the different risk groups.

For elderly patients

Elderly patients are often underrepresented or even excluded from clinical studies and concern has been raised regarding higher potential toxicity that may

result in dose reductions and a consequent lowering of activity for a given regimen. Although age did not remain an independent prognostic factor in our model, this factor led to the retrospective analysis of a large body of studies. Data collected from randomised trials [28] using fluoropyrimidine monotherapy reported no survival differences for patients below or above 70 years of age (3195 versus 629 patients). And patients above or below 70 years of age derived the same survival benefit of infusional over bolus 5-FU. In another study, no statistically significant difference in haematological and non-haematological toxicity was observed for patients under or over the age of 70 [29]. In a retrospective analysis using the data of 951 patients treated in two first-line studies for metastatic disease [30], a total of 201 patients were $\geqslant$70 years of age. Interestingly, grade III or IV neutropenia was more frequent in younger than in elderly patients (45% versus 37%) in the study comparing infusional 5-FU with or without oxaliplatin. The opposite (43% versus 60%) was observed in the study in which the bolus 5-FU/IFL regimen was compared to either IROX or FOLFOX4. Patients of all age groups derived the same survival benefit when the control and the experimental groups were compared.

We analysed 2691 patients entering four randomised trials comparing 5-FU-folinic acid with or without irinotecan either using a bolus 5-FU or an infusional 5-FU regimen [31]. A total of 599 patients were $\geqslant$70 years of age. In younger patients there was a clear demonstration that irinotecan improved the overall survival significantly while there was no survival difference in elderly patients. A more detailed analysis considering the used regimen indicated that the IFL regimen was particularly harmful for elderly patients and there appeared to be a benefit for patients between 70 and 75 years of age in favour of irinotecan treatment while this difference could not be observed in the group of patients above or equal to 75 years of age, which represented only 6.9% of the total population (185 patients). Thus, while infusional 5-FU in combination with either oxaliplatin or irinotecan appears to be beneficial for elderly patients, there is very limited data in patients above 75 years of age. It has also been mentioned with caution that patients entering clinical trials are highly selected for co-morbidity. This may be one of the explanations why age does not come out as an independent prognosticator in a multivariate analysis.

For patients with performance status 2

Indeed, the results of our multivariate analysis questioned the value of combination chemotherapy in patients with PS 2 especially if additional parameters such as elevated white blood cell count and more than one metastatic site are present. Thus, it would be worthwhile to know whether the higher toxicity associated with combination chemotherapy will definitely result in better treatment outcome.

The question of whether poor-risk patients with a PS of 2, which typically represent less than 10% of the total population of a clinical trial, will derive benefit from combination chemotherapy has recently been studied in a large analysis using data of 6286 patients from randomised trials investigating the role of combination chemotherapy either FOLFIRI (5-FU-leucovorin-irinotecan) or FOLFOX as compared to bolus infusional or IFL regimens [32]. These trials included 509 patients (8%) with PS 2. The overall survival was significantly shorter for PS 2 patients as compared to PS 0–1 patients (median 8.5 months versus 17.3 months; HR 2.18; $P < 0.0001$). All together, combination chemotherapy did prolong the overall survival for PS 0–1 patients as compared to monotherapy (15.2 months versus 16.9 months; HR 0.88; $P = 0.002$), and to the same extent (but not significantly) for patients with PS 2 (median 7.7 months versus 7.6 months; HR 0.88; $P = 0.27$). The benefit of overall survival, however, was clearly demonstrated if infusional 5-FU rather than bolus 5-FU was used in combination with irinotecan or oxaliplatin. In this case the overall survival did increase from 15.5 months to 18.8 months (HR 0.84; $P = 0.0001$) in PS 0–1 and from 5.4 months to 11.8 months (HR 0.69; $P = 0.0001$) in PS 2 patients. Thus, these data do suggest that the overall survival benefit derived from combination chemotherapy is larger for PS 2 patients than it is for PS 0–1 patients.

For the different clinical strategies

Patients with a potential for cure after shrinkage of metastases should be treated with combination chemotherapy probably independent of age and PS or any other definition of a risk group. These patients will most likely belong to the good-risk group (PS 0–1 plus other favourable prognostic factors).

Patients with disease related poor PS (not due to co-morbidities) should be offered combination chemotherapy upfront which will definitely prevent early progression, improve symptoms and has the potential of offering 2nd or even 3rd line treatment in the continuum of care.

The more debatable group of patients are those with good PS and treated with palliative intention. It will be the skill of the physician with his individual judgement

for the risk status of a given patient to decide on upfront combination or sequential treatment using the available anti-neoplastic agents and antibodies. Thus, if not the avoidance but rather the delay of neurotoxicity that might accompany a patient for more than 3 to 4 years, then this will be a quality of life achievement. For other patients the delay of potential alopecia induced by irinotecan in about 1/3 of patients to a later stage of the disease may be appropriate for some patients, and also the use of EGFR or VEGF antibodies to a time when the toxicity of these agents is better accepted may be indicated without compromising the survival.

Thus, the dogma of giving all available drugs to our patients is a gross simplification in everyday clinical decision making. In consequence, giving most or even all(!) available drugs together in first-line chemotherapy will definitely not fit every patient, if at all desirable, and may even be harmful [33], but intelligent risk-adapted use including the sequential approach, and depending on the strategy of the treatment, may be most appropriate.

Finally, our clinical parameters are powerful prognosticators and have been confirmed in several studies over several decades using different treatment regimens. Although data with EGFR or VEGF antibodies are lacking, all new potential molecular markers, unless they are predictive for response, should compete with clinical parameters before they are accepted as clinical decision making tools.

Conflict of interest statement

None declared.

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