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Can we predict toxicity and efficacy in older patients with cancer? Older patients with colorectal cancer as an example

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ABSTRACT

Colorectal cancer is a disease of the elderly. As older and frail patients are under-represented in clinical trials, most of the evidence available on treatment of older metastatic colorectal patients with cancer originates from pooled analyses of the older patients included in large prospective clinical trials and from community-based studies. The aging process is highly individual and cannot be based on the chronological age alone. It is characterised by a decline in organ function with an increased risk of comorbidity and polypharmacy. These issues can result in an increased susceptibility to the complications of both the disease and treatment. Therefore, evaluation of performance status and the chronological age alone is not sufficient, and additionally assessment must be included in the treatment decision process. In the present review, we will focus on clinical aspects of treating older and frail metastatic colorectal patients with cancer, but also on the present knowledge on how to select and tailor therapy for this particular group of patients.

Trial registration number: EudraCT 2014-000394-39, pre-results.

INTRODUCTION

Colorectal cancer (CRC) is a disease of the elderly with about 60% of patients with CRC aged 65 years or above and approximately one-third of the patients at least 75 years at the time of diagnosis.[1] There have been major developments in treatment options including both medical treatment and surgical options translating into a substantial survival improvement, however mainly in patients included in clinical trials.[2]

The survival improvement over time is also seen in the general metastatic colorectal cancer (mCRC) population. However, the improvement in outcome is much more pronounced in younger patients than in the older mCRC population.[3] In a population-based study of patients with mCRC, the median survival (mOS) was only 10.7 months.[4 5] This modest survival was primarily driven by a short mOS in patients older than 75 years of age and in a large number of patients not receiving any chemotherapy. The mOS was twice as long (21.3 months) in the subgroup of patients included in a clinical trial. Older patients with CRC are to a lesser extent referred for an oncological evaluation and they get oncological treatment less frequently than younger patients with CRC.[6]

In recent years the 'buzzword' in cancer therapy has been 'personalised therapy'—for example, to plan the precise therapy for the right person aiming to create a treatment plan most likely to be effective and with the lowest risk of toxicity for the individual patient. Often personalised cancer therapy is defined by cancer biology, for example, by predictive biomarkers. At present useful predictive markers are the RAS gene status for anti epidermal growth factor receptor (EGFR) therapy in patients with mCRC, mismatch repair status in adjuvant 5-flourouracil (5-FU) therapy in stage II CRC, and perhaps pharmacogenetics as UGT1A1 polymorphism for prediction of the toxicity of irinotecan.

A final definition of when a person is old is still not clear. According to WHO, most developed countries have accepted a chronological age of 65 years as a definition of 'older',[7] but in the literature the definition of older range from 60 up to 70 or even 75 years. This can be explained by the fact that chronological age not always matches physiological age. Aging is a complex process characterised by a progressive decline in the functional reserve of multiple organs and systems and thereby an increased

susceptibility to the complications of both comorbidities and cancer disease, as well as the treatment hereof. Furthermore aging also influences on physical, psychological and social resources. When treating older patients it is therefore important to realise that the aging process is highly individual and that an individual treatment plan in the elderly cannot be based on biological tumour markers and age alone—other tools must be included in the decision-making process.

In this review, we will focus on clinical aspects of treating older and frail patients with mCRC, but also on the present knowledge on how to select and tailor therapy for this particular group of patients.

TREATMENT OF OLDER OR FRAIL PATIENTS WITH MCRC

Standard therapy of patients with mCRC includes combination 5-FU based chemotherapy with irinotecan or oxaliplatin often given in combination with targeted agents.[8] Even though combination chemotherapy is often the choice for standard therapy, studies have shown that starting with monotherapy followed by new therapy immediately on progression may be a safe and effective strategy associated with low toxicity.[9 10]

Older and frail patients are under-represented in clinical trials,[11 12] and therefore much of the evidence available on treatment of older patients with mCRC originates from pooled analyses of older patients included in large prospective clinical trials and from community-based studies. This might be problematic, since they represent a selected group of fit patients with no or at least very limited comorbidity due to strict inclusion and exclusion criteria. Furthermore, comorbidity is often seen in the elderly population, and as a direct consequence, older patients often take more medications than younger patients. Thirty-five per cent of older patients with cancer take more than five prescribed medications daily, whereas this is only the case for 15% of patients younger than 70 years.[13] Such polypharmacy is associated with increased risk of adverse drug reactions, medication errors, non-compliance and hospitalisation.[14] Likewise, the risks of drug-drug interactions increase with the number of drugs taken. A retrospective chart review of 244 patients identified 769 potential drug interactions (PDIs) in 75% of patients and found PDIs to be strongly associated with non-hematological toxicity.[15] In another retrospective study of 172 Japanese patients receiving irinotecan, given either as monotherapy or as FOLFIRI, polypharmacy and reduced renal function were associated with severe irinotecan-related toxicity. The analysis was adjusted for patient-related data, including UGT1A1 genotype.[16] Furthermore, the function of several important organs such as liver, lung, kidney, heart and bone marrow, declines individually with age. In a Danish population-based study aiming to describe the prevalence of comorbidity in older newly diagnosed patients with cancer, it was found that moderate-severe renal disease was more prevalent in older patients with CRC than in the background population (OR 2.24 (95% CI 1.16 to 4.31)).[17] In the SOFT trial, where chemo-naïve patients with mCRC in good performance status (PS) were randomised to mFOLFOX6 plus bevacizumab or S-1/oxaliplatin plus bevacizumab, the incidence of grade 3–4 diarrhoea was increased (21% vs 6%) for patients treated with S-1/oxaliplatin in patients with impaired renal function (GFR less than 1·17 mL/s) compared to patients with a creatinine clearance of at least 1·17 mL/s.[18] Thus reduced kidney function often leads to increased toxicity in patients with cancer, and as older patients with cancer often have moderate-severe renal disease, focus on kidney function in this group of patients is highly demanded.

The general conclusions from subgroup analyses from pooled analyses of clinical studies are that efficacy and safety are maintained in older patients. In a retrospective analysis including 22 trials, it was found that efficacy of 5-FU based treatment did not differ between older and younger patients. In all, 3825 patients with mCRC were included, however only 16% of the study population were older than 70 years.[19] Similar pooled analyses of combination chemotherapy regimens have been performed as well. A study of FOLFOX with inclusion of 3742 patients with CRC (16% >70 years) from four clinical trials (in the adjuvant, first-line, and second-line settings) concluded that FOLFOX had the same efficacy and safety ratio in selected older patients compared to younger patients.[20] In an analysis of 2500 patients with mCRC included in four first-line randomised phase III studies of irinotecan/5-FU regimens, older patients (>70 years) had similar benefit and similar risk of toxicity compared to younger patients.[21]

However, these conclusions differ from the conclusions from community-based studies, where older patients (>65 years), experienced more treatment-related hospitalisations (21% vs 11%) and had a shorter mOS (19.1 months vs 24.5 months) than younger patients.[22] This discrepancy between results from the pooled analyses of randomised clinical studies and from population-based studies of un-selected patients with mCRC, probably reflects the selection of the robust older patients full-filling the inclusion criteria of randomised studies.

To avoid a narrow selection of fit older patients due to inclusion criteria, a few clinical studies have been designed to include exclusively older and/or frail cancer patient to obtain a more accurate image of older patients. A phase II study included 58 patients with mCRC with good PS (0–1) but aged 75 years or above (median 81 years). The patients received UFT+folinic acid (FOL). Grade 3–4 toxicities were observed in 55% of patients, primarily diarrhoea and other gastrointestinal toxicity, and half of the patient required dose reduction.[23] The median progression-free survival (mPFS) was 4.6 months and mOS was 13.0 months. In another phase II study, 51 patients with mCRC aged 70 years or more who were not candidates for

combination therapy were treated with capecitabine as monotherapy. It was concluded that capecitabine monotherapy was effective with a mOS of 11 months and toxicity modest with grade 3+4 toxicity in 12%.[24] The J-Blue study included 55 older Japanese patients with mCRC with a median age of 80 years in a phase II study of UFT, oral FOL (3 weeks on 1 week off) and bevazicumab every second weeks. Therapy was very well-tolerated with grade 3–4 toxicity observed in less than 10%. The most common reported toxicities were fatigue, nausea, stomatitis and diarrhoea. Response rate was 40%, mPFS was 8.2 months and mOS 23 months, and more than half (65%) of patients continued with second-line therapy.[25]

In another Japanese phase II study, the BASIC trial, 56 older patients with mCRC (>65 years) received S-1 and bevacizumab. S-1 was given days 1–28 in a 42 day cycle with bevazicumab every two weeks. The median age was 75 years and mPFS was 9.9 months. Median OS was 25.0 months. Therapy was discontinued in 18/56 due to toxicity. The authors concluded that S-1 plus bevacizumab is effective and safe for older patients.[26]

In the Spanish TTD study 66 older patients with mCRC were included. Nearly all patients had at least one comorbidity and half of the patients at least three comorbidities. Patients were originally treated with cetuximab (400 mg/m^2) and capecitabine at a dose of 1250 mg/m^2 twice daily. However, due to safety reasons the protocol was amended to give capecitabine at a dose of 1000 mg/m^2 twice daily (750 mg/m^2 in cases of moderate renal insufficiency). In the KRASwt population response was seen in 48% of the patients and mOS was 18.8 months.[27]

Doublet chemotherapy with capecitabine and oxaliplatin (CapeOX) was tested in a phase II study in the first-line setting in 50 patients with mCRC over the age of 70. Most of the patients had a PS of 0–1 (98%). Patients received full dose therapy (oxaliplatin 130 mg/m^2 and capecitabine 2000 mg/m^2) unless impaired renal function in which doses of capecitabine were reduced. The authors concluded that CapeOX was well-tolerated and with a clinical benefit.[28]

Many but not all randomised trials of palliative chemotherapy show a prolonged mOS in patients receiving doublets. However, these results are not validated in older patients. Two randomised studies evaluated this strategy in older patients with mCRC.[29 30] The FFCD 2001–2002 trial included patients aged 75 years or more and compared first-line monotherapy with 5-FU to FOLFIRI,[29] but found no significant difference in mPFS (5.2 months vs FOLFIRI 7.3 months, HR 0.84 (0.66 to 1.07), p=0.15) or mOS (14.2 vs 13.3 months, HR 0.96 (0.75 to 1.24)). As expected, the authors found that FOLFIRI was associated with an increased toxicity.

In the FOCUS2 study,[30] 459 previously untreated patients with mCRC, not considered candidates for full-dose standard therapy, were randomised to reduced dose monotherapy (5-FU or capecitabine) or reduced dose combination therapy (FOLFOX/CAPOX). The median age was 74 years (35–87) with 43% of the patients being older than 75 years. Dose escalation was recommended in patients with no or few side effects, however doses were only escalated in 37% of patients and more often in patients receiving monotherapy. Doublet with oxaliplatin increased response rate (from 13% to 35%) and there was a trend for improved progression-free survival with doublet chemotherapy (HR 0.84 (0.69 to 1.01), p=0.07) but no sign of improved mOS (HR 0.99 (0.81 to 1.18)).

A different strategy was used in the AVEX trial[31] in which 280 older fit patients with mCRC were randomised to capecitabine monotherapy with or without bevacizumab. Addition of bevacizumab significantly increased RR (from 10% to 19%, p=0.04) and prolonged mPFS (from 5.1 to 9.1 months; HR 0.53 (0.41 to 0.69)). Median OS was prolonged from 16.8 to 20.7 months but failed significance. Serious adverse effects were more common in patients receiving the bevacizumab primarily hypertension, haemorrhage and venous thromboembolic events, but in general the combination treatment was generally well tolerated in these older patients. The AVEX study thus showed a clinically meaningful benefit of bevacizumab when combined with monotherapy in older patients.

Thus, tolerability to chemotherapy is very various in different populations, and the question is how best to predict this to avoid severe complications to therapy, or to avoid under-treatment of fit older patients with mCRC.

HOW TO SELECT THE RIGHT TREATMENT FOR THE OLDER PATIENT?

The Eastern Cooperative Oncology Group (ECOG) or the Karnofsky performance status (PS) summarises the functional status of the patient with cancer and is used in the treatment-decision process of patients with cancer. However the evaluation of the PS is subjective and dependent on the individual treating physician. Furthermore, PS does not reflect true functional status of the older patients with cancer.[32] Thus, other tools must be included in the pretherapeutic evaluation of older patients with mCRC to distinguish between the frail or vulnerable and the fit older patients.

An acknowledged tool to make a more general assessment, and to describe the heterogeneity in older patients systematically, is comprehensive geriatric assessment (CGA). CGA is defined as 'a multidimensional, interdisciplinary diagnostic process focusing on determining an older person's medical, psychosocial, and functional capabilities to develop a coordinated and integrated plan for treatment and long-term follow-up'.[33] The domains assessed in a CGA are social status, comorbidity, functional status, cognition, depression, nutrition, fatigue, polypharmacy and geriatric syndromes (eg, dementia, delirium, falls, constipation and sarcopenia). A CGA thus assesses the patient's overall health status. Numerous tools have been developed for

identifying problems in each domain of the CGA. Examples are Activities of Daily Living (ADL), Timed-up-and-Go, Grip strength and ECOG PS, all assessing functional status. The original CGA used in geriatrics, comprises a geriatric intervention to improve performance in any domain. In the oncological setting focus has mainly been on the prognostic or predictive value of the assessment and not the intervention, and as a consequence, the International Society of Geriatric Oncology (SIOG) decided to use the term geriatric assessment (GA).[34]

The GA can supply the clinicians with detailed information about the older patient, locates problems not identified in a routine history or physical examination[34] and may predict treatment-related toxicity and mortality.[35 36] If a GA is successfully conducted in an oncological setting and the result is incorporated in the clinical decision-making, it can lead to significant changes in the cancer care.[37]

The knowledge on GA as well as screening tools, their cut-off points and predictive values needs further exploration as most of the studies in this regard are retrospective and based on small and often heterogeneous study populations. Owing to these study designs it was in two onco-geriatric reviews on GA up to 2012 not possible to make a meta-analysis on the effect of GA on treatment toxicity and overall survival.[38] To accommodate this issue prospective studies in larger and more homogenous study populations are wanted.[39]

As described, a GA is time-consuming and despite the recommendations from SIOG, a GA is not used on a regular basis in daily clinical practice in most institutions. Therefore, there is a growing interest in the use of shorter screening tools and models to identify patients in need of a GA or simply to replace it.[40] However, studies on these screening tools are often small and with very diverse study populations and they are often not comparable because of the different instruments they use.[38 41]

Below we describe the most promising screening tools for identifying possibly vulnerable older patients with cancer. SIOG has performed a systematic review of 17 different screening tests to determine which test was more prognostic of an impaired GA in older patients with cancer and found that the G8 and the Vulnerable Elders Survey (VES-13) were among the three most studied screening tools in older patients with cancer.[42] On this basis, we have chosen to describe the G8 and VES-13. Furthermore, they screen several components from the GA. The Flemish version of the Triage Risk Screening Tool (fTRST(1) and fTRST(2)) and Groningen Frailty Indicator (GFI) are alternative tools. Timed-up-and-Go (TUG) and grip strength (GS) evaluate functional status, are well studied and easy to perform. It should be stressed, that according to guidelines, these screening tools should be used to identify older patients with cancer in need of a GA. They are not recommended as tools to identify vulnerable or frail older patients with cancer alone.[34]

The G8 is an eight-item screening tool found to have great potential for identifying patients with cancer with a geriatric risk profile.[40 43 44] It takes approximately 5 min to perform and includes seven elements from the Mini Nutritional Assessment covering food intake, body mass index, weight loss, mobility, neuropsychological problems, number of medication, self-perception of health and in addition an age-related item. Thus several domains from the full geriatric assessment are covered. The score ranges from 0 to 17. A score≤14 is considered abnormal and should result in a GA.

In a non-randomised study, 1967 patients aged 70 or older were screened with the G8, and if it resulted in a geriatric profile a GA was conducted. The study reported that a GA revealed previously unknown geriatric problems in 51% of the patients, which resulted in a change in treatment decision for 25% of the patients. The assessment led to geriatric intervention in 26% of the patients.[40]

In a review by SIOG, the G8 was compared with GA in eight studies with findings of sensitivity >80% in six studies (range 65–92%) and specificity >60% in six studies (range 3–75%).[42] Furthermore, the G8 has been found to be predictive of functional decline,[43] and to be associated with chemotherapy-related toxicity[45] and overall survival.[43 46]

The VES-13 is a 13-item self-administered tool used to identify older patients with increased risk of health deterioration in the general population based on age, self-rated health and the ability to perform functional and physical activities. A score ≥3 is associated with an increased risk of functional decline or death within 2 years.[47] The patients will use about 5 min to fill in the tool. In a SIOG review, the VES-13 was compared to GA in 11 studies, in two of the studies showing a sensitivity >80% (range 39–88%) and specificity ranged from 62% to 100%.[42] The VES-13 was found to be associated with chemotherapy-related toxicity[45] and overall survival.[48]

TUG is a test used to assess the functional status of the older patient. The patient is observed and timed while getting up from an arm chair, walking 3 m, turning, walking back and sitting down again. Cutting-off value is defined as 20 s.[49] TUG was originally used in patients undergoing surgery for solid tumours, but it has also been tested in patients with cancer receiving chemotherapy. In 348 patients older than 70 years, scheduled for first-line chemotherapy, a GA including TUG was performed. It showed that older patients with a poor TUG (>20 s) had 2.5 times the odds of early death compared to those with a normal TUG.[50] It has also been demonstrated that slow TUG is significantly associated with higher risk of declining functional status in older patients during first-line chemotherapy.[51] Thus, TUG may be a useful tool in evaluating functional status in the older patient treated with chemotherapy.

The hand grip test is performed with a hand dynamometer and estimates strength in the upper extremity, and as hand grip strength correlates with other muscle

groups in the body, it can be used as a measurement for overall strength.[52] It has been found to be predictive for functional decline in the general older population, and in heterogeneous groups of patients with cancer it is significantly associated with overall survival.[53]

Besides from being among the most studied screening tools, G8 and VES13 also seem to have the highest sensitivity and specificity when compared to a full GA. The combination of the G8 and VES13 has showed an even better sensitivity for detecting risk of vulnerability than the two tools used alone.[54]

As perviously discussed in a recent editorial by Lembrecht Jørgensen and Pfeiffer[39] an important point is that even though GA performed by a geriatric specialist may induce an intervention in one of the examined domains which the older patient may benefit from, everyday life in the oncological clinic does not leave time for a full GA. Thus establishing a less time-consuming tool able to predict which older patients, who may benefit from and tolerate the treatment, would be essential and desirable.

CONCLUSION

Several screening instruments for prediction toxicity and efficacy in older and/or frail patients with mCRC are available but we still need more knowledge from prospective, preferable randomised trials in order to make evidence-based guidelines which can be used for daily clinical decisions.

As described above, some studies based exclusively on older and/or frail patients with cancer are published however to a much lesser extent than studies based on the young fit population. However, do the older patients with cancer want treatment and are they willing to participate in clinical trials? These are important questions to answer, to ensure that the information about treatment and trial participation is not influenced too much by personal values of the healthcare personnel.

Studies have shown that patients with cancer are much more likely to accept therapy with only a small chance of benefit than people who do not have cancer, including medical and nursing professionals.[55 56] Knowledge on older patients with cancer attitude to treatment is sparse, but a questionnaire survey performed among older French and American patients with cancer, showed that 70.5% and 77.8% of the American and French patients with cancer, respectively, were willing to accept aggressive chemotherapy with several side effects and nearly all patients (88.5% and 100%) were willing to accept mild chemotherapy with fewer side effects.[57]

It has been shown that when offered, older patients with cancer are as likely to participate in clinical trials as younger patients, but they did not actively seek the clinical trials themselves.[58] It is concluded that more appropriate studies must be designed to enrol older patients with cancer and clinicians needs to be aware of the opportunity and inform the patients.

In April 2015, a Nordic multicenter randomised trial was launched (EudraCT nr. 2014-000394-39). In this study older patients (≥70 years) with non-resectable mCRC, who are not considered candidates for standard full-dose combination therapy are included. Beside baseline standard clinical evaluations such as PS and routine blood-test, the G8, VES-13, TUG, Grip strength, Charlson Comorbidity Index and Quality of Life (EORTC QLQ-C30) will be performed. The patients are randomised to either a full dose monotherapy strategy (S-1 followed by irinotecan at the time of progression) or reduced dose combination therapy strategy (S-1 and oxaliplatin followed by S-1 and irinotecan).

It is important that new prospective studies like the present described, are launched continuously, to increase our knowledge on how to tailor treatment of older patients with mCRC, not only based on biological markers, but also on tolerability, thereby optimising treatment of this patient group.

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