Frailty in Metastatic Colorectal Cancer

Subjects: Oncology
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Colorectal cancer (CRC) is one of the main causes of cancer death in the elderly. The older patients constitute a heterogeneous group in terms of functional status, comorbidities, and aging-related conditions. Therefore, therapeutic decisions need to be individualized.

Frailty is a complex, multidimensional, and cyclical state of decreased physiological reserve resulting in a reduced capacity for adaptation and adaptability and greater vulnerability to stressors. The adverse health outcomes associated with frailty are summarized in disability and functional dependence, cognitive deterioration, increased hospitalization and institutionalization, intolerance to chemotherapy, instability of comorbidities, social exclusion, and decreased survival.

Keywords: metastatic colorectal cancer ; elderly

1. Introduction

The incidence and mortality from colorectal cancer (CRC) will increase in the coming decades, mainly due to the progressive aging of the population. The risk of being diagnosed with CRC increases with each decade of life. More than 75% of patients and more than 85% of deaths from CRC will be in patients older than 65 years [1][2]. The overall survival (OS) of patients with metastatic CRC (mCRC) progressively decreases according to the age at which it was diagnosed, from 23–31% three-year survival in patients under 60 to 5–11% in those over 80 years [3].

Therefore, the treatment of mCRC in geriatric patients is a challenge, where the benefit of chemotherapy must be balanced with the higher risk of developing toxicity [4].

Pharmacokinetics and pharmacodynamics of the drugs as well as the tissue tolerance can be altered with aging and secondarily, increase the treatment toxicity [5]. Other factors such as comorbidities and polypharmacy could also increase the risk of toxicity and interactions [6]. Although clinical trials provide most of the data about the efficacy and toxicity of chemotherapy in the elderly, these selected patients are hardly representative of the geriatric population in real life. In addition, there is a lack of data about the impact of chemotherapy in the clinical practice in this population.

Older age itself, without the evaluation of others factors, is often considered as a frailty sign and, therefore, perceived as a risk factor for chemotherapy-induced toxicity [7]. In this scenario, elderly patients could be undertreated, administered suboptimal doses or even omitting treatments, which may decrease efficacy [8][9].

2. Frailty in Oncology

Based on these data, the current consensus of oncologists suggests a mandatory assessment of frailty for all patients over 70 years or those younger people with significant involuntary weight loss in recent months (>5%) [10][11].

The US National Comprehensive Cancer Network and the International Society of Geriatric Oncology recommended adding a geriatric assessment (GA) to standard oncologic evaluation, addressed to detect frailty in elderly patients and help in the decision-making process regarding cancer treatment [12][13]. Most experts propose to evaluate the follow domains of GA in elderly cancer patients: functional status, comorbidity, cognition and mental status, chronic fatigue, social support, and geriatric syndromes. The scientific evidence currently available confirms that GA applied systematically to elderly patients modifies the final decisions of oncologists on the indication or intensity of cancer treatment in 20–45% of cases [14][15][16][17][18][19][20].

Multiple tools have been developed to assess frailty in cancer patients (Vulnerable Elders Survey 13, Flemish version of the Triage Risk Screening Tool, G8 questionnaire, Groningen fragility indicator, Balducci criteria, etc.). Most studies demonstrate the usefulness of geriatric tools and confirm that the most potent individual indicator for the risk of toxicity of

cancer chemotherapy is the functional status, evaluated especially by ability to maintain the instrumental activities of daily life, and for overall survival it is the nutritional status [20][21][22].

The geriatric criteria for assessing frailty proposed by Balducci and Exterman [23] classified elderly patients with cancer into three groups. The "fit" group had no significant comorbidities or geriatric syndromes and were independent for activities of daily living (ADL) and instrumental activities of daily living (IADL). The "medium fit" group had fewer than three comorbidities, had no geriatric syndromes, had fewer than four IADI limitations, and no ADL disabilities. The "unfit" group had any of the following conditions: three or more significant comorbidities, geriatric syndromes, more than four limitations of IADL, or ADL disabilities. The recommendations were to treat "fit" patients in the same way as younger patients, adjust treatment doses and/or use monotherapy in "medium fit" patients, and finally, contraindicate cancer treatment and intensify palliative care in "unfit" patients [2][20][23][24][25][26].

In recent years, two tools have been developed specifically aimed at determining the toxicity risk of chemotherapy in elderly patients [27][28]. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) identifies the risk of both hematological toxicity and nonhematological toxicity. This tool includes (a) different components of the GA, such as the comorbidity (Cumulative Illness Rating Scale for Geriatric patient), IADL (Lawton–Brody scale), polypharmacy (number of drugs), nutritional status (Mini Nutritional Assessment), the cognitive situation (Mini Mental State Examination), and the state of mind (Geriatric Depression Scale); (b) biomedical variables (diastolic blood pressure and lactate dehydrogenase); (c) intrinsic potential toxicity of chemotherapy; (d) Eastern Cooperative Oncology Group (ECOG) performance status. The development study of CRASH index identified cut-off points predictive of a high risk of chemotherapy toxicity in cancer patients older than 70 years [13][27]. The Cancer and Aging Research Group (CARG) developed a predictive model of chemotherapy toxicity risk, based on a multicenter cohort of cancer patients older than 65 years, who were systematically administered a GA. The CARG tool finally included different predictive indicators of toxicity risk, such as age, tumor origin, standard or reduced doses of mono or polychemotherapy, hemoglobin, creatinine clearance, falls in the last 6 months, hearing, autonomy to take medications, ability of walking a block, and maintenance of social activity. The combination of the scores assigned to these different variables allowed cut-off points to be established and patients with a potentially unacceptable risk of toxicity to be discriminated [28]. This score was subsequently validated in an external study [29].

3. Frailty in Elderly Patients with Metastatic CRC

Different clinical trials in elderly patients with mCRC confirm that the regimens based on 5-Flurouracil (5FU) in mono or polychemotherapy, or biological treatments (panitumumab, bevacizumab, cetuximab) have a similar effect to that observed in younger patients, although they warn about a greater likelihood of adverse effects. These studies included patients with an acceptable biological reserve condition, and no follow-up was established on patients excluded due to their frailty [30].

A recent clinical trial analyzed survival and cancer-specific mortality in elderly patients with early CRC and adjuvant therapy. A GA and the Balducci criteria were used to determine frailty in this study. Of a total of 195 patients, 28% were considered unfit, and the adjuvant therapy was contraindicated, and 29% were considered medium fit, and the adjuvant therapy was adjusted. The five-year survival according to frailty criteria was 74%, 52%, and 27%, for fit, medium fit, and unfit patients, respectively. Most of the unfit patients died early, mainly from non-oncological causes (2). This data provides very interesting information that could be extrapolated to the mCRC.

Different cohort studies confirm a 2.6 times higher risk of mortality in frail patients with metastatic CRC compared with fit patients [26][30]. A multicenter observational cohort study of mCRC patients older than 70 years, treated with chemotherapy or/and bevacizumab during a mean of 5.5 months, recorded severe adverse events in 50% of patients and an overall survival of 8.9 months. In multivariate analysis, poor performance status was predictive of severe toxicity and malnutrition was predictive of a significantly lower survival [22].

The CRASH and CARG tools can be extrapolated and useful for the determination of frailty and the risk of toxicity of chemotherapy in mCRC; although their validation studies did not specifically address for these cases, they included many patients in whom the cancer origin was intestinal (12% and 27% respectively). Recently, a model has been proposed to predict the risk of developing toxicity and early death in chemotherapy-treated colon cancer patients [31]. However, this model has not yet been validated.

A meta-analysis of 37 cohort studies with CRC patients confirms that comorbidity and frailty are strong indicators of survival, and concludes that GA might help the oncologist to make decisions about cancer treatment and the management of geriatric syndromes and multiple comorbidities [30].

On the other hand, a recent study indicates that when the GA is not taken into account for prescribing chemotherapy, 34% of unfit patients are overtreated, which is associated with more grade 3–4 toxicity than those receiving treatment adapted to fragility (42% vs. 31%; $p < 0.05$) (9). In addition, recently, two randomized clinical trials evaluating the impact of GA vs. standard of care on chemo toxicity in older adults with cancer showed the integration of multidisciplinary GA-driven interventions reduced the incidence of grade 3–5 chemo-related toxicity by 10–20% [32][33].

In summary, despite there being few data from research in mCRC, there is a wide consensus that the assessment of frailty should be incorporated into the usual clinical history obtained by the oncologist, in those patients over 70 years of age or in younger people with a weight loss of more than 5% in recent months. The GA is the most complete evaluation tool for assessing frailty. Patients rated as high frailty will have a high risk of toxicity, a lower survival, and most will die from causes other than cancer. In patients with intermediate frailty, there is no formal contraindication to chemotherapy, but dose adjustment and the use of monotherapy should be considered, as well as favoring decision-making shared with the patient based on objective data. Finally, the assessment of frailty can also help to establish a multidisciplinary care plan that includes attention to comorbidity, geriatric syndromes, nutritional status, psychological impact, and socio-family support in those patients with greater needs.

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