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Review article

Inclusion of elderly or frail patients in randomized controlled trials of targeted therapies for the treatment of metastatic colorectal cancer: A systematic review

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ABSTRACT

Treatment of metastatic colorectal cancer (mCRC) has been modified since the launching of targeted therapies. Colorectal cancer (CRC) is common in elderly patients; their representation in randomized controlled trials (RCTs) is thus crucial. This study aimed to evaluate and quantify the inclusion of elderly/frail patients in RCTs of targeted therapies in mCRC.

A systematic review using Medline, Scopus, Cochrane Database and ISI Web of Science was performed to identify all phase II/III RCTs of bevacizumab, cetuximab, panitumumab, regorafenib and aflibercept in mCRC until January 2015. Two reviewers independently performed studies selection, and data extraction. The protocol was registered in Prospero (CRD42015016163).

Among 1,369, identified publications, 54 RCTs were selected. Nine RCTs (17%) excluded elderly patients; median age of the included population was <65 years old in 50 RCTs (93%). Twenty RCTs (37%) excluded frail patients, and many RCTs excluded patients with uncontrolled hypertension or heart failure, patients treated with specific drugs (mainly anticoagulants), and patients with inadequate creatinine clearance.

Elderly/frail patients are underrepresented in RCTs studying targeted therapies in mCRC, and those elderly patients included in RCTs do not reflect well the general elderly population with mCRC because of the exclusion criteria. RCTs results concerning targeted therapies can be inferred only to relatively healthy elderly subjects.

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1. Introduction

Cancer is a major cause of morbidity and mortality worldwide [1]. This is expected to increase over the next few decades, partly due to the aging of the population. More specifically, colorectal cancer (CRC) is the third most frequent cancer [1,2]. The estimated number of new cases in 2012 was 1,360,600 with a median age at diagnosis of 68 years [3,4]. In the United States, while the risk of developing CRC for patients less than 65 years old is 17.9 per 100,000 persons, it increases to 201.1 cases per 100,000 in patients aged 65 or older. Moreover, 33.7% of cases are diagnosed among people aged 75 or older [4]. Epidemiological data from the general population with metastatic CRC (mCRC) are not available. Yet, as metastases frequently appear years after the diagnosis of the primary tumor (metachronous mCRC) [5], it is expected that the median age at the diagnosis of mCRC is even higher than that of CRC.

Since 2005, new drugs (targeted therapies) have been approved by US and European authorities for the treatment of mCRC: bevacizumab, cetuximab, panitumumab, regorafenib and aflibercept [6,7]. According to guidelines, the standard of care in first-line mCRC treatment is a targeted therapy combined with conventional chemotherapy [6,7].

Elderly patients are generally underrepresented in randomized controlled trials (RCTs). In 2004, Talarico et al. [8] evaluated the inclusion of elderly patients in RCTs related to cancer therapy registered in the US Food and Drug Administration database and conducted between 1995 and 2002. In the 55 identified RCTs (7 for CRC), patients aged 65 years or older were significantly fewer than in the general population with cancer (36% *vs.* 60% respectively; $p < 0.001$). This underrepresentation was even worse in patients aged 75 years or older, which represented 9% of the RCTs population *vs.* 31% of the general population with cancer. During the same timeframe, Lewis et al. [9] found comparable differences for age (32% of patients aged ≥65 years in the RCTs *vs.* 61% in the general population) in 495 US National Cancer Institute-sponsored clinical trials. In this study, the difference in age was even greater for RCTs in the treatment of CRC.

Even if the underrepresentation of elderly patients is well admitted by the medical community, it has rarely been studied and quantified. To our knowledge, this was never investigated for RCTs of targeted therapies in mCRC. This question is important because the gap between the population included in RCTs and the general population with mCRC could impact the external validity of data resulting from these studies and their utilization to elaborate guidelines [7]. For these reasons, this systematic review aimed to evaluate and quantify the inclusion of elderly and/or frail patients in phase II and III RCTs that have studied targeted therapies available for the treatment of mCRC.

2. Methods

2.1. Search Strategy and Selection Criteria

Phase II or III RCTs on bevacizumab, cetuximab, panitumumab, regorafenib and aflibercept in mCRC were identified by searching scientific publications in Medline, Scopus, Cochrane Database and ISI Web of Science, until January 2015 without language or date restriction (see search strategy in Appendix A). References of meta-analyses retrieved through the systematic search were checked for additional references (snowballing procedure). Studies were considered eligible if they met the following criteria: phase II or III RCTs, at least one arm treated with specified targeted therapies, and evaluation of these targeted therapies in patients with mCRC for indications currently approved by US and European authorities.

Two independent reviewers (AG and PN) first screened the title and abstract of retrieved records. Studies considered meeting the eligibility criteria were selected for full-text review. A third independent reviewer (FS) resolved the disagreements between the two main reviewers. The protocol of this systematic review was registered in Prospero: international prospective register of systematic reviews (CRD42015016163).

2.2. Data Extraction

All available documents (main publication, *post-hoc* publications, study protocols, *clinicaltrials.gov*) were used for data extraction. AG extracted the information related to RCT characteristics (outcomes, recruitment period, treatment line, blinding, treatment arms, phase, primary tumor site, metastatic sites), inclusion and exclusion criteria, and patient characteristics, namely: age, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), gender, primary tumor site, metastatic sites, and comorbidities.

Median age, mean age, range, proportion of patients aged ≥65 years, and proportion of patients aged ≥75 years were extracted for each arm and for the overall population of each study eligible for this review. In case of missing data, the main investigator of the RCT was contacted to provide data about median age, range, number of patients aged 65 years or older and 75 years or older. An electronic database for the data extraction was created using EpiInfo™. PN reviewed and validated all extracted data.

2.3. Data Synthesis and Analysis

Frailty of included patients was evaluated through the ECOG-PS score. When only the Karnofsky score was available, a correspondence with the ECOG-PS was established according to Oken et al. [10].

As there is no consensus about elderly and frailty definitions in literature, we choose two cut-off points for analyses: aged <65 *vs.* ≥65 years and aged <75 *vs.* ≥75 years for elderly; and ECOG-PS <1 *vs.* ≥1 and ECOG-PS <2 *vs.* ≥2 for frailty.

A descriptive analysis was performed: number and proportion of patients in each category were presented for each of a selected characteristic. When RCT characteristics were described (*e.g.*, inclusion and exclusion criteria), the denominator for descriptive statistics was the number of included RCTs; when patients' characteristics were described (*e.g.,* ECOG-PS, primary tumor site), the denominator was the total number of included patients in all RCTs with available data. Overall population of each included study was considered. When this information was not available, the number of patients of each arm was summed.

The proportion of RCTs including patients with a median age ≥65 years or ≥75 years was calculated using the number of included RCTs as denominator. For all RCTs with available data, the proportion of patients aged ≥65 years or ≥75 years was calculated by using the number of included patients. The distribution of these proportions was described using the median, minimum and maximum. The proportions of patients aged ≥65 years or ≥75 years were also calculated by grouping the RCTs according to the year of first inclusion, and then compared to the proportion of elderly patients at CRC diagnosis estimated according to Surveillance Epidemiology and End Results (SEER) in the US [4]. The same methodology was applied for the proportions of