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Review article

A review and assessment of currently available data of the EGFR antibodies in elderly patients with metastatic colorectal cancer

Gerardo Rosati[a,*], *Giuseppe Aprile*[b], *Giovanni Gerardo Cardellino*[b], *Antonio Avallone*[c]

[a]*Medical Oncology Unit, S. Carlo Hospital, Potenza, Italy*
[b]*Departments of Oncology, University and General Hospital, Udine, Italy*
[c]*Gastrointestinal Medical Oncology Unit, National Cancer Institute G. Pascale, Napoli, Italy*

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ABSTRACT

Although the number of elderly patients is increasing each year, this population has been under-represented in clinical trials. At the same time, the survival of patients with metastatic colorectal cancer has been improving, not only because of improvements in chemotherapy, but especially because of the addition of monoclonal antibodies (bevacizumab, cetuximab and panitumumab). Therefore, it is necessary to define the role of these new drugs in the elderly population, a group that is heterogeneous and consists of those who are fit and able to tolerate all therapies equally as well as younger patients and unfit individuals who should only given best supportive care or therapies specifically modulated for them. Today, although data from phase II–III studies have helped to establish the role of bevacizumab in the elderly, few trials have studied anti-epidermal growth factor receptor (EGFR) antibodies in the same population. This review presents the results of studies carried out with anti-EGFR agents, with a hope that more trials will be carried out with these drugs in the elderly in the future.

Contents

* *Corresponding author*. Tel.: +39 971 612273; fax: +39 971 613000.
E-mail address: oncogerry@yahoo.it (G. Rosati).

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1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the third leading cause of death from cancer in Western countries. As mortality from cardiovascular disease and other non-cancer causes declines, elderly patients will have an increased risk of developing bowel cancer which has a median age of onset of 71 years at present [1]. This will result in the need to modify cancer services, with an exponential growth in social and economic issues over the coming years.

Moreover, the definition of elderly patients is challenging for medical oncologists. There are frequent discrepancies between physiologic and chronologic age, and many older people have several comorbidities that require careful assessment and, if necessary, individualized treatment approaches [2,3].

Through a comprehensive geriatric assessment that evaluates the patient's functional status, comorbidities, polypharmacy, nutritional status, cognitive function, emotional function and social support, oncologists can distinguish between those patients who are fit and those who are frail. The former group can be treated in the same way as younger patients, whereas the latter group should receive personalized treatments or should be given exclusive best supportive care (BSC) [4]. However, this is complicated by a huge debate in the literature about how frail patients should be defined, and how to differentiate frailty from comorbidity and disability [5,6].

A meta-analysis published some years ago indicated that patients with metastatic CRC receive the greatest survival benefit during the course of treatment when given fluoropyrimidines, oxaliplatin and irinotecan [7]. The addition of monoclonal antibodies (bevacizumab, cetuximab and panitumumab) to chemotherapy has further improved results in terms of response rate and overall survival (OS) [8–10]. However, the elderly are not sufficiently represented in clinical trials at present, and it is therefore difficult to extrapolate the results and extend them to all of this population.

Although in the past few years the potential benefit of bevacizumab in the elderly has become clear through prospective clinical trials and retrospective analyses [11,12], this has not happened in tandem with the use of epidermal growth factor receptor (EGFR) inhibitors.

The aim of this review is to systematically report results from studies using cetuximab and panitumumab in the elderly compared with those in younger patients and to determine differences between the two groups, both in terms of efficacy and tolerability.

2. Cetuximab

Cetuximab is the first monoclonal antibody introduced into clinical practice that binds competitively to the extracellular domain of EGFR. This chimeric immunoglobulin G_1 (IgG_1) can also elicit immunologic events that occur in treated patients: antibody-dependent cellular cytotoxicity, cross talk among immune cells including natural killer cells and dendritic cells and generation of tumor antigen-specific T lymphocyte responses [13]. Table 1 summarizes efficacy and safety data of cetuximab in the elderly.

The role of cetuximab in the first-line treatment of elderly patients with advanced CRC has been reported in two phase II studies conducted by the Spanish Cooperative Group for the Treatment of Digestive Tumors [14,15].

The first of these studies evaluated the efficacy and safety of cetuximab as a single agent in 41 fit elderly patients never previously treated for metastatic CRC. Patients had a median age of 76 years and, although many of them had concomitant comorbid conditions including vascular disorders and metabolism abnormalities such as diabetes, they had a Karnofsky performance status (PS) of 80–100. Treatment compliance appeared well because the median dose intensity was 245.5 mg/m^2/week and use of the drug was postponed because of skin toxicity in only 26.8% of patients; however, this was probably because the median duration of treatment was only 57 days. The results in terms of clinical response, time to progression and OS appear disappointing, but they are clearly influenced by the fact that patients were not selected at diagnosis for *RAS* status because the study was started in 2005, when it was not yet known that mutated patients should be excluded from treatment. In a post-hoc analysis performed on 23 patients for whom tumor tissue was available to determine *KRAS* status, seven of 18 patients with wild-type (WT) *KRAS* were progression-free at 12 weeks, whereas four of five patients with mutant *KRAS* progressed during the same period. Twenty-seven of the 41 patients (65.9%) received single-agent capecitabine and irinotecan or oxaliplatin-based combinations after progression on cetuximab. Skin toxicity was frequent and observed in 29 patients (70.7%); however, only five cases (12.2%) were reported as grade 3. Other adverse events, as asthenia, diarrhea, nausea and anorexia, were serious (grade 3/4) in <5% of patients. No toxic deaths or hypersensitivity infusion reactions were recorded. Although the authors found a correlation between efficacy and skin rash as in other studies, the small size, the low number of patients who responded and the fact that the difference did not reach statistical significance ($p = 0.163$) did not allow any firm conclusions to be drawn on this statement. After disease progression, a substantial number of patients (34%) had refused chemotherapy or were treated with capecitabine alone. Nevertheless, this study shows that cetuximab has intrinsic activity and can be used as first-line treatment in elderly patients who refuse chemotherapy and require a therapy that has limited toxicity.

In the second study cetuximab, administered weekly, was associated with capecitabine at a dose of 1250 mg/m^2 twice daily (bid), 2 weeks on and 1 week off. The trial results were weakened because *KRAS* status was determined in 58 of the 66 patients (88%) and the protocol was amended for safety reasons after the inclusion of the first 27 patients reducing the dose of capecitabine to 1000 mg/m^2 bid. The primary endpoint of the study was to assess clinical responses, and these were in the range of those obtained with oxaliplatin- or irinotecan-based combination chemotherapy in the elderly population [16]. The same considerations can also be made with progression-free survival (PFS) and OS. These data appear interesting considering that the median age of patients was 77 years and, although their PS was 80–100, 54% of them had three or more comorbid conditions. The most significant toxicity was paronychia, which was severe in 29.6% of patients and responsible for the amendment of the protocol.