



Italian survey on cetuximab-based therapy of elderly patients with metastatic colorectal cancer

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Abstract

Purpose There is no consensus on the use of cetuximab in elderly patients with metastatic colorectal cancer. To this end, a survey was carried in 17 Italian oncology centers.

Methods The centers answered a 29-item questionnaire structured as follows: (i) demographic characteristics; (ii) medical history; (iii) assessment of RAS/BRAF mutations and DPD/UGT polymorphism before treatment; (iv) treatment schemes and side effects; (v) geriatric assessment and customization of treatment.

Results One-third of patients are over 80 years old. The RAS/BRAF mutational status is not primarily evaluated by 17.6% of the centers, while DPD and UGT polymorphism is not evaluated by 82.4% and 76.5% of the centers. The most common therapeutic scheme is cetuximab/FOLFIRI and diarrhea is the main cause of suspension/reduction of treatment. The 70% of centers use systemic tetracyclines for skin toxicity. The 23.5% of the centers do not carry out any geriatric evaluation before the start of the therapy and those who perform it prefer the G8 (70.6%) and VES-13 (29.4%) scales.

Conclusions Greater efforts should be made to improve the evaluation of the patient both about mutational and genetic procedures with geriatric evaluation. As for cetuximab in elderly patients, randomized studies are needed to provide guidance to physicians.

Keywords Cetuximab · Elderly patients · Metastatic colorectal cancer · Survey

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and it represents a major burden for patients, caregivers and healthcare national systems [1]. Its incidence shows a steady progression, from one million new cancer cases estimated in 2006 to 1.4 million cases in 2012 [2].

The number of older patients with metastatic CRC (mCRC) is also constantly increasing. This is due to the extension of life expectancy, obtained mainly due to improved treatment for other life-threatening diseases.

Regarding their treatment, the geriatric evaluation with the systematic use of appropriate scales and quality of life care (QoL) have led to greater adherence to therapy and, ultimately, to improved survival [3].

However, the older patients are little represented in clinical trials [4]. Although the use of epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab is a marked progress of therapy with improvement of overall survival (OS) and progression-free-survival (PFS), as reported in major phase III trials [5, 6], the data appear less convincing when extrapolated to the older population both in terms of efficacy and toxicity [7, 8]. Nevertheless, a review on cetuximab evidenced that cetuximab shows positive results on older patients, with a PFS between 2.9 and 8.9 months and an OS between 7 and 30 months [9]. This great variability is probably due to the fact that cetuximab was used in various ways, both in the first-line

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and in the subsequent lines, alone or in combination with FOLFIRI (irinotecan plus 5-fluorouracil/leucovorin) or FOLFOX (oxaliplatin plus 5-fluorouracil/leucovorin). In addition, the studies were often carried out without a systematic evaluation of the mutational status of RAS and BRAF. In view of this scarcity of data, we have drawn up a survey that aims to collect evidence of the cetuximab use in older patients in selected centers in Italy.

Patients and methods

The objective of the survey is to collect information on the management of the older patients (i.e., over 70 years of age) with mCRC. The survey was carried out between December 2017 and January 2018 and involved 17 university and hospital oncology Italian centers. The clinicians were invited by the coordinator on the basis of their particular experience gained on this topic. They received via email a questionnaire on the management of older patients consisting of 29 items (Table 1) and exploring five areas concerning the management of the older patient with mCRC: (i) demographic characteristics of the survey population; (ii) medical history of patients; (iii) assessment of RAS and BRAF mutations as well as DPD and UGT polymorphism before treatment; (iv) treatment schemes and side effects; (v) geriatric assessment and customization of treatment. The questions that make up the survey include pre-specified, numerical or qualitative answers. Answers were collected in a central database. The statistical analysis was of a descriptive nature and was carried out at Fullcro S.r.l. in Rome. In the descriptive analysis, the categorical variables were reported through absolute and percentage frequencies and, graphically, through pie graphs representing the percentage frequencies. The statistical analysis was conducted using Statistical Package for Social Science (SPSS) software version 2.3. The survey was conducted according to the Italian regulations on surveys.

Results

The survey was conducted in 17 centers across Italy, thus involving the entire national territory (Fig. 1). Fifteen of the 17 centers (88.2%) are public, 2 (11.8%) are private and affiliated to Italian National Healthcare Service. Four of the 17 structures (23.5%) are university centers and the remaining 13 (76.5%) are oncology centers of general hospitals. The clinicians involved in the survey, each representing each center, answered all the questions they were asked.

Demographic characteristics of the survey population

Including in their entirety, the extrapolated data for all analyses refer to more than 1600 patients treated in the last 5 years in the 17 centers involved. Seven centers (41.2%) report having treated more than 100 patients on average in 1 year; when the figure is referred to last 5 years, the number of centers that declare having treated more than 100 patients doubles (14 centers; 82.3%). As for age distribution, the majority of patients (from 33 to 60% of the survey population in the different centers) are between 70 and 75 years old. Figure 2 shows the stratification of the study population by age and center. In the reference population there is no clear gender preference: 7 centers (41.2%) report female preferences; 3 centers (17.6%) report male preferences; 7 centers (41.2%) report the same distribution. Regarding ethnic group, 15 centers (88.2%) report a clinical history, which refers only to patients of Caucasian origin, while only 2 centers (11.8%) report to have cases referring to patients of mixed ethnicity.

Medical history of patients

Nine centers (52.9%) report that there is no prevalence of left or right localization of the primary tumor, 8 centers (47.1%) report a left prevalence (from splenic flexure onwards). Sixty percent of the centers report that in more than half of the cases (60%) patients have more than one metastatic site. The metastatic localizations observed are in descending order of frequency the following: liver, lungs, bones, lymph nodes, peritoneum and ovaries. Regarding the surgical procedures, the centers state that 45% of the patients underwent surgery to remove only the primary tumor; in 15% of cases, both the primary tumor and a secondary location were removed; only metastatic surgery was performed in 10% of patients; the remaining 30% of patients underwent palliative surgery or no surgery.

Assessment of RAS and BRAF mutations and DPD and UGT polymorphism

A significant percentage of the centers (17.6%) do not evaluate the mutational status of RAS at the diagnosis of metastatic disease, but only subsequently; among the reasons indicated there are the patient's status, the spread of the disease and the belief that not necessarily an older patient, even if RAS wild-type (wt), should be treated with anti-EGFR in the first-line. A similar picture emerges when the evaluation of the mutational status of BRAF is considered; in this case, the percentage of centers that do not perform it at

Table 1 Survey administered to the centers

No.	Question	No.	Question
1	In your institution, what is the number of elderly patients with mCRC treated per year?	16	In clinical practice, do you consider it mandatory to search for polymorphisms of the UGT before beginning antineoplastic treatment?
2	In your institution, what is the number of elderly patients with mCRC treated in the last 5 years?	17	Indicate, by ordering 1–5, which of the following treatment regimens you use most frequently as the first-line starting from last 5 years: cetuximab + FOLFIRI, cetuximab + FOLFOX, cetuximab + irinotecan; cetuximab, others
3	In your clinical practice, what is the percentage distribution of reference population (elderly with mCRC) by age group (total 100%)?	17.1	Indicate, by ordering 1–5, which of the treatment regimens listed in question 17 you use most frequently on the subsequent treatment lines starting from last 5 years
4	In your clinical practice, what is the percentage distribution of elderly patients with mCRC by gender in the last 5 years?	18	Based on your experience, by ordering 1–6, indicate which is the most frequent reason to discontinuation of the treatment schemes listed in question 17
5	In your clinical practice, what is the percentage distribution of the reference population (elderly with mCRC) by ethnic group? (total 100%)?	19	Based on your experience, by ordering 1–6, indicate which is the most frequent reason to dose reduction of the treatment schemes listed in question 17
6	In your clinical practice, what is the percentage distribution of elderly patients with mCRC per site of disease?	20	In your clinical practice, do you use rating scales to categorize the elderly patient? If YES, in which percentage do you use rating scales to categorize the elderly patient?
7	In your clinical practice, in the elderly patient, at the time of diagnosis of metastatic disease do you assess the mutational status of RAS? If NO or NOT ALWAYS, what are the reasons?	20.1	Indicate which are the fast geriatric evaluation screening tools you are using: G8, VES-13, others?
8	Have there been any increases in the evaluation of the mutation status of RAS in the last 5 years in elderly patients with mCRC?	20.2.	Do you use the CGA rating scale for the complete geriatric assessment of your patients? If YES, please state in which percentage do you perform a complete geriatric assessment
9	In your clinical practice, in the elderly patient, at the time of diagnosis of metastatic disease do you assess the mutational status of BRAF? If NO or NOT ALWAYS, what are the reasons?	21	Has the use of geriatric assessment tools increased over the past year? If yes, please indicate in what percentage you use the following geriatric rating scales
10	Have there been any increases in the evaluation of the mutation status of BRAF in the last 5 years in elderly patients with mCRC?	22	Has the value of PS (performance status) influenced the choice of cetuximab?
11	In your clinical practice, what is the percentage distribution of elderly patients with mCRC by number of metastatic tumour sites?	23	Indicate, in order from 1 to 6, the factors that led you to choose a monotherapy
12	Indicate, ranking from 1 to 9, which are most frequent metastatic localizations of the primitive tumour	24	Indicate, in order from 1 to 6, the factors that led you to choose a combination therapy
13	In your clinical practice, what is the percentage of elderly patients with mCRC who have undergone an operation?	25	In your clinical experience, do you believe that over time there has been an improvement in the compliance despite of skin toxicity? If YES, with which strategies among the following?
14	In your clinical practice, on what percentage of RAS wt patients have you used therapies with cetuximab in all treatment lines?	26	Do you use tetracyclines in your elderly patient with mCRC for skin reaction?
14.1	In your clinical practice, on what percentage of RAS wt patients have you used therapies with cetuximab in first-line treatment?	27	Do you use growth factors in your elderly patient with mCRC for haematologic toxicity?
14.2	In your clinical practice, on what percentage of RAS wt patients did you use therapies with cetuximab in the second or subsequent treatment line?	28	In the elderly patient with mCRC in which there are no clinical conditions that prevent the foreseen dosage, do you customise the treatment? If YES, how?
15	In your clinical practice, do you consider it mandatory to search for polymorphisms of the DPD before beginning treatment with fluoropyrimidines?	29	What proportion of elderly patients with mCRC have undergone more than one line of treatment?



Fig. 1 Centers participating in the survey

diagnosis rises to 35.3% (Fig. 3). The reasons given are the heavy burden of the disease and the need to start a therapy as soon as possible, not compatible with the time necessary to obtain the results of molecular diagnostics. Other centers report evaluating BRAF only in patients enrolled in clinical trials. Many centers (64.7%) report that RAS evaluation has become more frequent in older patients in the last 5 years; this percentage rises to 82.4% for BRAF. Most centers do not evaluate the polymorphism of the DPD gene (82.4%) before an antineoplastic treatment including

fluoropyrimidine and the polymorphism of the UGT gene (76.5%) before irinotecan treatment.

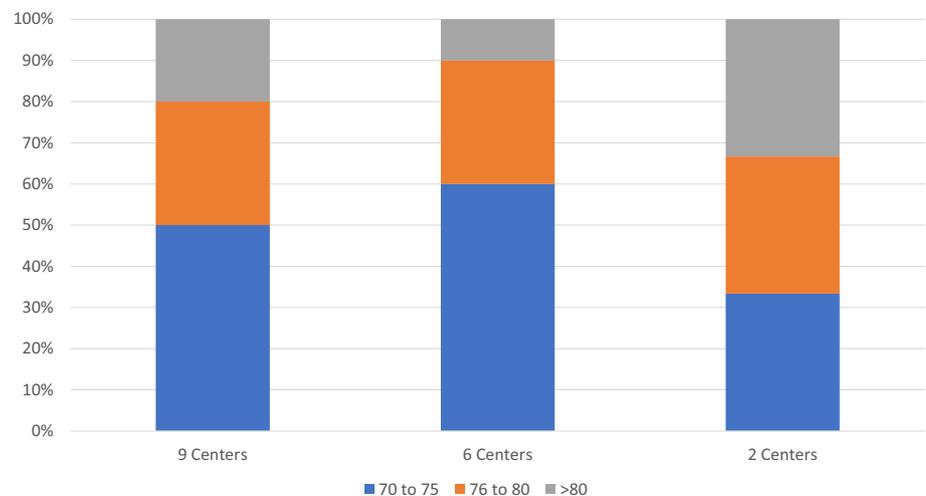
Treatments schemes and side effects

Only four centers (23.5%) use cetuximab routinely (i.e., in > 80% of cases) in all treatment lines for RAS wt patients. The most used schemes in the first-line are FOLFIRI or FOLFOX plus cetuximab. Cetuximab in monotherapy is reported to be fourth in frequency order for the first-line and third for the following lines (Table 2). The majority of centers (70.6%) report to have used more than one treatment line in more than 50% of their patients. For as concerns the reasons for treatment discontinuation or dose reduction, diarrhea is the first reason for cetuximab plus FOLFIRI; dermal and neurological toxicity is the most frequent reason for discontinuation and dose reduction for cetuximab plus FOLFOX; finally, the most frequent reason for discontinuation of cetuximab in monotherapy is dermal toxicity. Almost all the centers (94.1%) report that they use tetracyclines to reduce skin toxicity; they observe that the management of the skin toxicity has improved in the last years and this induced an improvement of patients' compliance. Seventy percent of centers use tetracyclines for the systemic prophylaxis of skin toxicity and 58.8% use topical treatments (mainly antibiotics and or topical steroids). Almost all centers (88.2%) use growth factors to counteract hematological toxicity.

Geriatric assessment and customization of therapy

About one quarter (23.5%) of the centers do not carry out any geriatric evaluation before the start of therapy, while half of the centers do not use the Comprehensive Geriatric Assessment (CGA) scale, preferring faster tools such as the G8 (70.6%) and the Vulnerable Elders Survey VES-13 (29.4%) scales (Table 3).

Fig. 2 Stratification of the study population by age



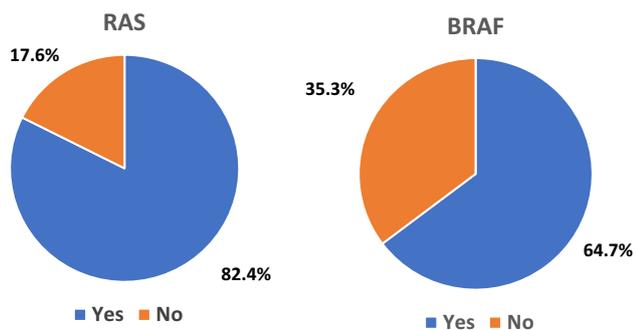


Fig. 3 Percentage of centers performing the assessment of the mutational status of RAS and BRAF from the beginning of the treatment

Table 2 First and subsequent lines of treatment

Rank	First line	Subsequent lines
1	Cetuximab + FOLFIRI	Cetuximab + irinotecan
2	Cetuximab + FOLFOX	Cetuximab + FOLFIRI
3	Cetuximab + irinotecan	Cetuximab and cetuximab + FOLFOX
4	Cetuximab	Other
5	Other	

Table 3 Percentage of centers performing the geriatric assessment and assessment scales used

No geriatric assessment	Geriatric assessment with CGA	Geriatric assessment with other assessment scales (50%)	
23.5%	26.5%	G8	VES-13
		70.6%	29.4%

According to 64% of centers, the use of geriatric evaluation scales has increased in the last year and 76.5% of centers report that the decision to use cetuximab is influenced by the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS). PS is claimed to be the most important factor influencing the choice between monotherapy and combination therapy. More than 60% of centers (64.7%) customize the therapy of older patients through adjustment of posology (reduction of maximal dosage or therapy start at reduced dosage).

Discussion

This survey has limitations and strengths intrinsic to the methodology. While the first are represented by the fact that the participants reported their experience without a detailed

consultation of the patients' medical records, the strengths are the participation of centers throughout the country, which offers a complete overview of the Italian therapeutic approach with the collection of the direct perception of doctors. Indeed, some of the results are in line with international literature.

A significant percentage of centers do not systematically search for the mutational status of RAS and BRAF at the diagnosis of metastatic disease and this suggests that many clinicians do not consider the use of an anti-EGFR antibody as mandatory in first-line setting. The main reason seems to be the need to start a systemic therapy as soon as possible, which is often not compatible with the necessary time to obtain the results of molecular diagnostics. However, although the oncologists interviewed report an increase in the evaluation of RAS and BRAF status in recent years, this conviction could be explained, even in the case of patients without RAS e BRAF mutation, on the basis of the results of recent phase III studies that have not sufficiently clarified if, among patients with KRAS wt untreated advanced or metastatic colorectal cancer, there was significant difference in overall survival between the addition of cetuximab or bevacizumab to chemotherapy as initial biologic treatment [10, 11]. A second explanation could be sought in the demonstration of the predictive effect of tumor location, with a greater effect of chemotherapy plus anti-EGFR antibodies only for patients with left-sided tumors [12, 13]. Third, the elderly constitute an extremely heterogeneous population with different prognosis, therapies tolerance and treatment motivation. Even when they are not candidates for oxaliplatin-based or irinotecan-based chemotherapy regimens, it has been shown that the combination of bevacizumab and capecitabine is effective and well-tolerated [14]. The same may be not stated when capecitabine is associated with cetuximab. Keeping in mind their combined effects on skin and nail toxicity, which led to a reduced dose of capecitabine or even both within a phase II study, one could believe in a negative interaction between these drugs [15]. These concerns are reinforced by the publication of data from a recent small randomized phase II study in which, although capecitabine and cetuximab shown better efficacy results compared to cetuximab monotherapy, their combination increase the risk of serious infections, has a negative impact on QoL and treatment refusal, and more treatment stoppings were caused compared to cetuximab alone [16]. Therefore, considering that cetuximab alone prolongs survival in chemotherapy-refractory patients [17], some centers consider more reasonable to proceed with sequential administration of cetuximab after acquired resistance to chemotherapy alone or in combination with bevacizumab, avoiding adverse effects.

Although there is greater awareness of the usefulness and importance of selecting patients through geriatric scales, over three quarters of clinicians (76.5%) consider the PS as

the most used system for deciding the most appropriate therapy for the specific type of older. Actually, the assessment of the functional status by the ECOG scale is not as effective in older patients as in the younger population, because comorbidities in the elderly interfere with this parameter [18]. Comorbidities alter the results of therapies by delaying the diagnosis of cancer, decreasing the use of chemotherapy, increasing the toxicity of the treatments, and acting as a competing cause of death. Only validated tools, as the CGA, could provide an objective evaluation and assist the oncologists in the decision-making process distinguishing patients who are fit and those that are frail [19]. Nevertheless, among the centers that routinely perform a correct geriatric evaluation, half of the cases do not use the CGA, preferring more rapid instruments such as the G8 or VES-13 [20, 21].

Physicians convinced of the usefulness of the RAS test in the first instance and that select the fit patient through the geriatric scales do not have particular concern about the side effects with FOLFIRI or FOLFOX plus cetuximab. However, it should be emphasized higher rates of grades 3–4 diarrhea and neutropenia in these circumstances and confirming the importance of close monitoring of serious adverse effects in older patients [5, 22–24]. In this context, the determination of polymorphism of the DPD and UGT genes from the beginning of chemotherapy plus cetuximab may be even more important in this population. It is well known in fact that a deficiency of DPD, traceable between 3 and 15% of cases, is responsible for fluoropyrimidines' severe toxicities in 10–40% of patients and toxic deaths in 0.2–0.8% of patients, while UGT1A1* 6 polymorphisms is associated with an increased risk of irinotecan-induced neutropenia in cancer patients [25, 26]. Nonetheless, about 80% of clinicians consulted do not consider it necessary to undertake routine screening of DPD deficiency or UGT polymorphism in the elderly. Anyhow, side effects remain the first reason for stopping chemotherapy, and in 64% of cases the doctor customizes the therapy, mostly not reaching the maximum theoretical dosage even in patients who do not have any special contraindications.

Most clinicians perform therapies after the first-line in just over 50% of cases. When possible, this choice should be discouraged because the OS is influenced by subsequent treatments, as already demonstrated in the literature [27].

Seventy percent of the centers use tetracyclines and 58.8% use topical treatments for systemic prophylaxis of cutaneous toxicity due to EGFR inhibitors administration, in accordance with the results of studies that has shown that a pre-emptive skin treatment regimen based on skin hydration, sunscreen, topical steroids and doxycycline is well tolerated, reduces the incidence of specific skin toxicity and patients report an improvement in QoL [28, 29]. Almost all centers (88.2%) use granulocyte-colony stimulating factors (G-CSF), in accordance with European Organisation

for Research and Treatment of Cancer (EORTC) guidelines that recommend special attention to patients, as elderly (≥ 65 years) receiving a chemotherapy regimen with high risk of febrile neutropenia, as it could be for schemes such as FOLFOX or FOLFIRI plus cetuximab [30]. So, the survey suggests that both the management of skin reaction and hematological toxicity has improved; there is a greater awareness about skin and hematologic problems when it comes to a more fragile population such as the elderly.

Conclusion

Our analysis suggests that greater efforts should be made to improve the evaluation of the patient both concerning the mutational status and with regard to a complete geriatric evaluation. In connection with the use of cetuximab in older patients, there is a need for randomized studies with a robust methodology to provide data that give clear guidance to physicians.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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