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Cetuximab for treatment of metastatic colorectal cancer

G. Cerea*, R. Ricotta, I. Schiavetto, M. R. Maugeri, A. Sartore-Bianchi, M. Moroni, S. Artale & S. Siena

The Falck Division of Medical Oncology, Ospedale Niguarda Ca' Granda, Milan, Italy

In the past decade the median overall survival of patients with metastatic colorectal cancer has increased from 12 to more than 20 months, mostly due to the new chemotherapeutic agents, irinotecan and oxaliplatin. Most recently, targeted therapies, that inhibit specific cancer pathways and molecules, have shown promising results in the treatment of patients with metastatic colorectal cancer and other solid tumors. One of the most studied targets for anticancer therapy is the epidermal growth factor receptor (EGFR), which is overexpressed in a variety of malignancies. Cetuximab, an anti-EGFR chimeric monoclonal antibody, has shown clinically meaningful antitumor activity in patients with metastatic colorectal cancer in several clinical trials. Efforts of physicians and researchers are currently directed towards the identification of predictive factors (clinical or molecular) of clinical outcome, with the aim of both optimizing the therapeutic index and dealing with increasing costs of these new compounds.

Key words: colorectal cancer, targeted therapies, predictive factors, cetuximab

introduction

Worldwide, colorectal cancer is the fourth most commonly diagnosed malignant disease, with an estimated 1 023 000 new cases and 529 000 deaths each year [1]. The median overall survival of patients with metastatic colorectal cancer has increased from 12 months with chemotherapy regimens based on 5-fluorouracil (5-FU) to 21 months in the past decade [2]. This improvement in survival is mainly due to the introduction of two chemotherapeutic drugs, oxaliplatin and irinotecan. Once a patient's cancer becomes refractory to these agents, however, there were, until 2005, poor treatment options with demonstrated activity.

In recent years, a new strategy has been evaluated for patients with cancer: targeted therapies that inhibit specific cancer pathways and molecules involved in tumor growth and progression. One of the most studied targets for anticancer therapy is the epidermal growth factor receptor (EGFR), a transmembrane glycoprotein member of the ErbB receptor family. In response to the binding of ligands, epidermal growth factor (EGF) and transforming growth factor alpha (TGF-α), the receptor homodimerizes or forms heterodimers with other members of the ErbB family, thus stimulating phosphorylation of intracellular kinases and initiating downstream signaling cascades. EGFR is over-expressed in 77% of colorectal cancer and is involved in tumor growth and metastasis through the interference in mechanisms of cell proliferation, apoptosis and neo-angiogenesis [3].

activity of cetuximab in metastatic colorectal cancer

The primary therapeutic methods of EGFR targeting are monoclonal antibodies and small-molecule tyrosine kinase inhibitors [3]. Several clinical trials have shown the antitumor activity of cetuximab, a chimeric (murine and human) monoclonal antibody, in patients with metastatic colorectal cancer. A pioneer phase II study of weekly cetuximab and irinotecan in 121 patients who had colorectal cancer that was refractory to fluorouracil and irinotecan found a 22.5% response rate [4]. To determine whether the antitumor activity was due to synergy between the two drugs or due to the independent activity of cetuximab, Saltz et al. enrolled 57 patients with EGFR-expressing colorectal cancer that progressed on CPT-11 treatment in a phase II trial. All patients were treated with single agent cetuximab. Of all patients, 9% had a partial response and 35% had a minor response or stable disease [5]. Subsequently, in the European phase II randomized BOND trial, Cunningham et al. [6] enrolled 329 patients with metastatic colorectal cancer that progressed after CPT-11 based therapy. Patients received either a combined therapy with CPT-11 and cetuximab or a monotherapy with the monoclonal antibody. The combined therapy with cetuximab and CPT-11 resulted in greater efficacy than the single-agent therapy, with a higher objective response rate (22.9% versus 10.8%), overall

*Correspondence to: Dr G. Cerea, Ospedale Niguarda Ca' Granda, Piazza Ospedale Maggiore 3, 20162 Milano, Italy. Tel: +39-0264442290; E-mail: giu.ce@katamail.com

disease control rate (55.5% versus 32.4%), and a prolonged time to progression (4.1 versus 1.5 months).

At the present time efforts are directed towards incorporating the use of cetuximab to an earlier stage of the course of the disease, such as in the first-line or in the adjuvant setting. Noteworthy among these, is a recent phase II study by Diaz-Rubio et al. [7], which showed a high response rate (72%) to cetuximab in combination with oxaliplatin-based chemotherapy. Another multicenter randomized phase III trial (CRYSTAL trial) is evaluating the combination of cetuximab with irinotecan-based chemotherapy. Several phase III studies are ongoing to evaluate the use of cetuximab with chemotherapy and others targeted therapies such as bevacizumab, gefitinib and erlotinib in metastatic colorectal cancer.

prediction of clinical outcome

Several authors have attempted to identify, so far in a retrospective manner, the elements that can predict the response or clinical benefit from therapy with cetuximab. This area of research is motivated by the need to optimize the therapeutic index (mostly because of cutaneous side-effects) as well as the need to deal with increasing costs of new targeted therapies. As an example, the combination of irinotecan and cetuximab, approved in US and Europe for patients progressing on irinotecan-based therapy, costs (exclusively for drugs) approximately $30 790 for an 8-week course [8].

In the European BOND trial, the expression of EGFR evaluated by immunohistochemistry (IHC) in terms of staining intensity as well as of percentage of EGFR-expressing cells, did not correlate with objective tumor response [6]. Intriguingly, Chung and colleagues showed four major responses in 16 patients treated at Memorial Sloan-Kettering Cancer Center with EGFR-non expressing tumors by IHC [9]. These findings suggest that IHC as a method for EGFR expression is a poor indicator of which tumors are most sensitive to targeted therapy with cetuximab.

Dermatologic toxicity, a typical adverse event of cetuximab as well as of other anti-EGFR clinical agents [10], appeared to be associated with an increased response and survival in patients with colorectal cancer treated with cetuximab or with other histologies treated with EGFR-targeted drugs [6, 10]. In the BOND trial, the response rates in patients with skin reactions after cetuximab treatment were higher than those in patients without skin reactions (25.8% versus 6.3% in the combination therapy group and 13.0% versus 0% in the monotherapy group). However, in our opinion, skin rash should be regarded as a surrogate rather than a truly predictive marker.

The molecular mechanisms underlying clinical response or resistance to monoclonal antibodies are unknown. In a recently published paper, Moroni et al. [11] screened for genetic changes in EGFR, or its immediate intracellulars effectors, tumors from 31 patients with metastatic colorectal cancer treated with cetuximab or panitumumab. Specifically, they assessed the EGFR copy number and the mutation profile of the EGFR catalytic domain and of selected exons in KRAS, BRAF and PIK3CA. The authors showed that patients with metastatic colorectal cancer who have a clinical response to anti-EGFR treatment have a significantly increased EGFR copy number on the assessment of individual tumor samples by fluorence *in situ* hybridization (FISH). Furthermore, mutations in EGFR catalytic domain and in immediate downstream effectors did not correlate with response. This finding, that requires validation in prospective randomized studies, is a candidate strategy to identify patients with colorectal cancer who are likely to benefit the most from EGFR-targeted therapies.

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