Colorectal cancer: cetuximab, KRAS, BRAF, PIK3CA mutations and beyond

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“Latest advances include genotyping-based selection of patients in the metastatic setting without mutations in KRAS, BRAF, NRAS and PIK3CA genes for treatment with cetuximab.”

With a long-term disease-free survival rate of 35% after multimodal treatment of stages II and III colorectal cancer (CRC) and mean overall survival (OS) of approximately 20 months in the metastatic setting, progress in the management of CRC is faster and the prognosis is better than for other gastrointestinal tumors [1]. Over the last 10 years systemic-targeted therapy has led to hope for further survival improvement. However, strong evidence has demonstrated that cetuximab, the most popular anti-EGF receptor (EGFR) antibody, is ineffective in unselected patients with metastatic CRC (mCRC).

Recently, retrospective studies have only shown a potential survival benefit for patients without mutations in KRAS, BRAF and PIK3CA genes. These data recreate an enthusiasm for the efficacy of cetuximab, panitumumab and other anti-EGFR inhibitors based on patients selected by genotyping. However, considering the retrospective nature of these studies and the complexity and heterogeneity of solid cancers including CRC, how optimistic can we be for the effectiveness of the present generation of targeted agents? What are the expectations for the emerging complete CRC genome sequencing and efforts to predict the inference of complex dynamic signaling pathway networks that are dysregulated in CRC?

Systemic treatment
Strong evidence suggests that systemic chemotherapy improves survival of patients with CRC. A chemotherapeutic regimen with fluorouracil-based treatment combined with either irinotecan or oxaliplatin has been the standard of care in early and advanced CRC. Specifically, in the metastatic setting, chemotherapy has improved OS to more than 20 months [2]. In the adjuvant setting, it provides a clear OS benefit. Indeed, a recent study by the Adjuvant Colon Cancer Endpoints Group analyzed the data set from 18 trials and more than 20,800 stage II or III colon cancer patients testing fluorouracil-based adjuvant therapy. At a median follow-up period of 8 years, this chemotherapeutic regimen significantly reduced the risk of recurrence after complete surgical resection (R0) to 35%. Given that recurrence events rarely occur after 8 years or more following treatment, the authors point out the importance of adjuvant chemotherapy to improve cure rates [3]. Promises for further OS rate improvement have provided recent exciting translational research on targeted agents.

Cetuximab & panitumumab
Recently, five randomized controlled trials testing the safety and efficacy of the addition of cetuximab or panitumumab to chemotherapy alone or plus bevacizumab

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in mCRC have been published [4-8]. No survival benefit was seen due to the addition of cetuximab to chemotherapy in unselected patients. Taking lessons from other major cancer types, such as non-small-cell lung cancer (NSCLC), with genotyping-based benefit derived from targeted treatment, efforts have been focused on genotyping-based patient selection. This research has demonstrated that among patients receiving cetuximab, those with KRAS mutations had worse survival than those without mutations (KRAS wild-type). Table 1 summarizes the results of these studies, which included 3896 patients. The addition of these anti-EGFR antibodies only significantly improved progression-free survival (PFS) for the KRAS wild-type disease. As a result, recent guideline recommendations suggest the consideration of these antibodies, and in oncological practice, decision-making treatment for cetuximab is based on KRAS status. Usually, cetuximab is given only to patients with KRAS wild-type mCRC.

However, even for noncarriers of KRAS mutations, the response rate to cetuximab is not high and a only proportion of patients benefit from this treatment. Therefore, the next step was to look at whether additional genotyping for other genes contributing to signal transduction from EGFR to the nucleus would further improve patient selection. BRAF mutation status was evaluated to assess cetuximab efficacy in mCRC. In the CAIRO2 trial, 559 patients were assigned to chemotherapy plus cetuximab or chemotherapy alone, genotyping for BRAF mutations was carried out for all patients. PFS and OS were significantly better among patients without BRAF mutations compared with those with BRAF mutations [9].

Other than the KRAS and BRAF mutation status, additional genotyping for NRAS and PIK3CA mutations was evaluated to assess the efficacy of cetuximab in patients with chemotherapy-refractory mCRC. In this retrospective study, 773 primary tumor DNA samples had sufficient quality DNA and were included in mutation frequency analyses; mass spectrometry genotyping of tumor samples for KRAS, BRAF, NRAS and PIK3CA was carried out centrally. All of the patients were treated with cetuximab between 2001 and 2008 and were gathered from 11 centers in seven European countries [10]. In total, 40.0% (299 out of 747) of the tumors harbored a KRAS mutation, 14.5% (108 out of 743) a PIK3CA mutation, 4.7% (36 out of 761) harbored a BRAF mutation and 2.6% (17 out of 644) harbored an NRAS mutation. De Roock and colleagues, while confirming the negative effect of KRAS mutations on outcome after the addition of cetuximab, demonstrated that BRAF, NRAS and PIK3CA exon 20 mutations were significantly associated with a low response rate [10]. Objective response rates could be improved by additional genotyping of BRAF, NRAS and PIK3CA exon 20 mutations in a KRAS wild-type population.

Efficacy & limitations
What conclusions can we draw from the aforementioned randomized clinical trials and retrospective studies?

First, strong level I evidence provides sufficient data demonstrating that cetuximab or panitumumab are ineffective in unselected patients with mCRC. Second, several retrospective analyses suggest an increased response rate and a survival benefit when cetuximab is added to chemotherapy in genotyping-based selection of patients. Potentially, patients in the metastatic setting without mutations in KRAS may benefit from the addition of cetuximab to chemotherapy. Third, further genotyping for BRAF, NRAS and PIK3CA among KRAS wild-type may increase the response rate to cetuximab.

However, in the absence of evidence from Phase III randomized controlled trials only enrolling patients without KRAS mutations, and with a primary end point of OS, caution is suggested for the use of cetuximab in a day-to-day clinical practice. Until such data become available, careful consideration of potential benefits and harms by adding cetuximab to chemotherapy for mCRC and balance of benefits and adverse effects in individual patients for the decision-making treatment appears to be useful in an effort to improve patient's oncological outcomes.

Beyond current targeted therapy
Currently, more rigorous criteria are required, carefully balancing the risks and benefits of new agents in medical practice [11]. For example, emerging evidence on intratumoral heterogeneity suggests that although most cancer cells are sensitive to these agents, resistant small cancer cell subpopulations rapidly proliferate, causing tumor regrowth and new metastases [12]. Moreover, although they are limited, the use of cetuximab or panitumumab increases the risk of adverse events, including skin reactions, infusion-related reactions and diarrhea [4-8].

Could these anti-EGFR antibodies improve survival and cure rates in the adjuvant setting? It is unclear whether these biologics reduce risk of recurrence in stage II and III CRC, thus improving survival. The absence of OS benefit in the metastatic setting is suggestive of the inability of the treatment to eliminate all cancer cells, and reduces the expectations for clinical success in the adjuvant setting. However, the limited tumor burden with the presence of only micrometastatic disease in stages II and III might be eliminated by the therapeutic effect of the biologic agents. Therefore, we should await the results of near-complete or ongoing trials (bevacizumab: NSABP C-08, AVANT, E5202, Quick and Simple and Reliable Collaborative Group-2, NCCTG, N0147; cetuximab: PETACC-8) for definitive conclusions. The...
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Emerging goals

The major goals of emerging translational research are to develop and validate more effective drugs other than the currently used targeted agents and to tailor these drugs to the right patient. These two goals of personalized medicine might become realistic through the question of whether these targeted drugs have a recurrence-delaying, curative or no effect in the adjuvant treatment of CRC still remains crucial [3].

Future perspectives

The significance of understanding and predicting dysregulated signaling pathway networks in cancer is increasingly guiding novel therapeutic strategies on targeted therapy to inhibit downstream signal transduction in most solid cancers, including CRC.

Explosion with genome sequencing technology

The ability of massively parallel sequencing technology to identify causal (driver) mutations involved in cancer and to understand the functional role of mutant genes along with rapidly falling sequencing costs and improved sequencing quality data have revolutionized biology and biomedical sciences. Dozens of complete sequence human genomes have been published and more than 200 are due to be published [18]. Recently, three fully sequenced cancer genomes, including breast cancer, lung cancer and melanoma have been published [19]. Despite this genomic revolution, clinical implications in disease risk prediction, prevention and treatment are currently modest [5–19].

This lack of translating genomic research discoveries into oncological application is now explained by cancer’s extreme complexity. Indeed, at the end of the first postgenomic decade, emerging genomic data revealed the high complexity and heterogeneity of the disease, which explains the clinical limitations of classic single-gene molecular research [12–22]. It appears that for most patients, multiple mutations deregulate several signaling pathways and the oncological outcome is driven more by complex molecular and signaling pathway interactions than a simple mutant gene–phenotype relationship [22–26]. The more we learn, the more we understand the complexity of life diversity and complex disease pathogenesis and evolution, such as cancer [27–29]. The implications of a genomic revolution into medicine and oncology are limited. In order to move forward in the future, Collins considers five key lessons: personalized medicine, technology, policy, partnerships and pharmacogenomics [17]. Venter emphasizes the need for research on linking genotype to phenotype, and points out that because of myriad phenotypic traits, more powerful computational strategies will be needed to link the phenotype to the genotype [18].
sequencing cancer genomes [17–19] and predicting complex non-linear bioenvironmental dynamic systems [24–26]. Although the goal of achieving the completion of a mutation catalogue for each cancer type appears realistic in the following years, the great challenge is how to use novel statistics methods and powerful computational strategies to derive inferences on noisy dynamic chaotic biological and environmental systems towards next-generation biomarkers and targeted agents [30,31]. More recently, a new method has been proposed to overcome the big challenge of predicting noisy nonlinear ecological dynamic systems [32]. Such intellectual efforts raise optimism for reaching the goal of a bioworknet-based generation of drugs and biomarkers.

Despite advances in improving understanding of CRC initiation, progression and metastasis [33,34], prevention and treatment of this major cancer still remains a major health problem. Current advances in integrating clinical data into genotyping to predict oncological outcomes using novel network modeling and statistics may open new avenues in the management of CRC and the major complex human diseases [18,32,35–40].

Conclusion

Rapid progress in molecular biology and oncology has improved the survival rates of patients with CRC. The latest advances include genotyping-based selection of patients in the metastatic setting without mutations in KRAS, BRAF, NRAS and PIK3CA genes for treatment with cetuximab. However, because of resistance to treatment, failure rates still remain high and many patients die of the disease. Sequencing cancer genomes and using systems biology approaches represent exciting promises for the future in order to save the lives of patients who currently die from the disease.

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