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Targeted therapy in metastatic colorectal cancer – An example of personalised medicine in action

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ABSTRACT

In metastatic colorectal cancer (mCRC), an improved understanding of the underlying pathology and molecular biology has successfully merged with advances in diagnostic techniques and local/systemic therapies as well as improvements in the functioning of multidisciplinary teams, to enable tailored treatment regimens and optimized outcomes. Indeed, as a result of these advancements, median survival for patients with mCRC is now in the range of 20–24 months, having approximately tripled in the last 20 years. The identification of *KRAS* as a negative predictive marker for activity of epidermal growth factor receptor (EGFR)-targeted monoclonal antibodies (mAbs), such as panitumumab (Amgen, Thousand Oaks, USA) and cetuximab (ImClone, Branchburg, USA), has perhaps had the greatest impact on patient management. This meant that, for the first time, mCRC patients unlikely to respond to a targeted therapy could be defined ahead of treatment. Ongoing controversies such as whether patients with *KRAS* G13D- (or BRAF V600-) mutated tumours can still respond to EGFR-targeted mAbs and the potential impact of inter- and intra-tumour heterogeneity on tumour sampling show that the usefulness of *KRAS* as a biomarker has not yet been exhausted, and that other downstream biomarkers should be considered. Conversely, a predictive biomarker for anti-angiogenic agents such as bevacizumab (Genentech, San Francisco, USA) in the mCRC setting is still lacking. In this review we will discuss the discovery and ongoing investigation into predictive biomarkers for mCRC as well as how recent advances have impacted on clinical practice and ultimately the overall cost of treatment for these patients.

Introduction

Until relatively recently we believed that cancer could essentially be treated using the same combinations and sequences of locoregional (surgery and/or radiotherapy) and systemic (chemotherapy) treatments in all patients. However, we are now in a transitional period where we are embracing a more personalised approach to cancer management. The heterogeneous nature of cancer means that personalised medicine (i.e. tailoring therapy to an individual patient) is a promising approach for maximising efficacy and minimising the toxicity of treatment. It also facilitates efficient healthcare delivery and generates cost savings because treatment is only given to those likely to benefit and so costs associated with drug wastage, hospital resource utilisation and side-effect management are reduced. To successfully deliver personalised medicine, it is necessary to have a clear understanding of the pathology and molecular underpinnings of a disease, as well as the associated clinical characteristics that define different patient sub-populations with different outcomes in relation to a given treatment. Identifying the optimum treatment strategy also involves an understanding of a patient's medical history, disease status, and sometimes, their socio-economic situation, and consideration of the wider healthcare framework, such as the availability of hospital resources and reimbursement.

The ultimate goal of personalised medicine is to define a disease sufficiently to enable identification and treatment of only those

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patients most likely to respond. Although personalised medicine is almost exclusively discussed in the context of targeted therapies, chemotherapy also has the potential to be tailored to individual patients. Advances in genomic and proteomic technologies and the implementation of major collaborative studies such as the human genome project and genome-wide association studies (GWAS), have already generated much data and are leading to the identification of many biomarkers – a characteristic that can be objectively measured and evaluated as an indicator of pathogenic processes or treatment responses. Biomarkers have been identified for: early detection/risk stratification (diagnostic markers); the likely course of a given disease (prognostic markers); and prediction of treatment safety/efficacy outcome (predictive markers).

The principle of targeted therapy was first proposed by Paul Ehrlich more than 100 years ago, when he coined the term 'magic bullet'.[1] Immunohistochemistry (IHC) provided one of the first opportunities to personalise medicine and was effectively used in breast cancer to identify patients with tumours expressing oestrogen and/or progesterone receptors, who were candidates for 'targeted' hormonal therapies like tamoxifen (AstraZeneca, Delaware, USA). Furthermore, since its discovery more than 30 years ago,[2]hybridoma technology has enabled production of large amounts of monoclonal antibodies (mAbs) targeted to specific tumour antigens, and has led to a vast array of new diagnostic and therapeutic options. These advances are already revolutionising cancer screening, drug development and treatment selection, and are major factors in personalising medicine in the 21st century. This concept has gained momentum in recent years with the development of other successful therapies such as imatinib mesylate (Novartis, New Jersey, USA)[3] for chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours (GIST) and trastuzumab (Genentech, San Francisco, USA)[4] for breast and gastric cancers. These agents target specific molecular alterations (abnormal protein tyrosine kinase activity for imatinib, overexpression of human epidermal growth factor receptor-2 [HER-2] for trastuzumab), which are now used as predictive biomarkers of response, thereby allowing these drugs to be targeted to individuals with the appropriate tumour characteristics.

Colorectal cancer (CRC) is perhaps one of the best examples of how an increased understanding of disease molecular biology has successfully merged with improved diagnostic techniques, advances in local/systemic therapy, and improvements in the functioning of multidisciplinary teams, to enable tailored treatment regimens and optimized outcomes.

Evolution of personalised therapy in metastatic CRC (mCRC)

Globally, CRC is the third most commonly diagnosed cancer in males and the second in females[5] and is the second leading cause of cancer mortality in the United States, accounting for 9% of all cancer deaths.[6] Approximately one-quarter of CRC patients have metastases at diagnosis and a further 33–50% develop metastases over their disease course.[5,7] Surgical resection offers the possibility of cure for a small minority of patients with mCRC and isolated metastases.[8] Management by a multidisciplinary team including, for example, surgeons, oncologists, interventional radiologists, radiotherapists, and nurses, increases the number of patients able to undergo potentially curative treatment and has consequently improved patient survival.[7,9] Together, advances in local and systemic therapy have led to improvements in survival[10] with median survival in mCRC increasing from approximately 8–24 months[9,11] over the last 20 years. The improvements in survival times in mCRC patients diagnosed between 1990 and 2006 at two large specialised institutes are exemplified in Fig. 1.[12] The availability of new cytotoxic and targeted therapies and the implementation of personalised medicine have been instrumental in this process.[13]

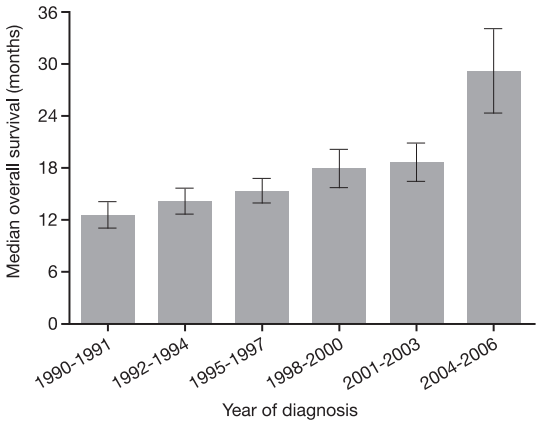

Fig. 1. Median overall survival for patients with metastatic colorectal cancer treated at the M.D. Anderson Cancer Center and the Mayo Clinic by year of diagnosis (error bars are 95% confidence intervals).[12] Reprinted with permission © 2009 American Society of Clinical Oncology: Kopetz S, et al. J Clin Oncol 2009; 27(22):3677–3683. All rights reserved.

Evolution of systemic therapy for mCRC

Chemotherapy has been standard care for mCRC patients for many years, and is based mainly on the use of three agents: 5-fluorouracil (5-FU; APP Pharmaceuticals, Schaumburg, USA), irinotecan (Pfizer, New York, USA)[14,15] and oxaliplatin (Sanofi-Aventis, Bridgewater, USA).[16,17] Infusional 5-FU regimens-such as FOLFIRI[18] or FOLFOX[19] have better efficacy than earlier bolus 5-FU regimens and currently provide the backbone of therapy.[20] Capecitabine (Genentech, San Francisco, USA),[21] an oral formulation of 5-FU, is also available.

Whilst the vast majority of biomarker research has focussed on targeted therapies, efforts are continuing to identify predictive markers of response or resistance to chemotherapy. Up to now, however, there are only a few noteworthy examples. Although results are somewhat conflicting, high thymidylate synthase (TS) expression has generally been linked with poorer outcomes during 5-FU-based therapy,[22,23] and 5-FU adjuvant treatment may also be ineffective in tumours with microsatellite instability.[13] Irinotecan was one of the first chemotherapy agents to be dosed based on the recipient's pharmacogenomics; reduced irinotecan doses should be considered in patients homozygous for the *28 variant form of UGT1A1 as they are unable to clear irinotecan as quickly as normal and, therefore, suffer more severe haematological side effects.[24] Furthermore, homozygosity for the *28 variant form of UGT1A1 has been linked with improved efficacy of FOLFIRI.[25]

The most promising predictive marker of resistance to oxaliplatin is excision repair cross-complementing C1 (ERCC1) expression,[26] and although there is currently no standard test available, it is possible that ERCC1 testing may become routine in mCRC patients in the future. Genetic differences in the glutathione transferase pathway have also been suggested to lead to higher rates of neurotoxicity during oxaliplatin therapy,[27] however, this is yet to be confirmed and has not yet impacted on clinical practice. In addition, a FOLFOX response predictor has recently been constructed based on gene expression profiles of responding and non-responding patients.[28] Initial results suggest that the overall accuracy of this predictor is high (92.5%) and therefore it may offer the possibility of selecting patients who would benefit from FOLFOX.