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Overview of biomarkers in metastatic colorectal cancer: Tumour, blood and patient-related factors

Stephen J. Clarke [a,*], Christos S. Karapetis [b], Peter Gibbs [c], Nick Pavlakis [a], Jayesh Desai [c,d], Michael Michael [d], Niall C. Tebbutt [e], Tim J. Price [f], Josep Tabernero [g]

[a] *Department of Medical Oncology, Royal North Shore Hospital, Pacific Highway, St Leonards, NSW 2065, Australia*
[b] *Flinders University and Flinders Medical Centre, Bedford Park, SA 5042, Australia*
[c] *Department of Medical Oncology, Royal Melbourne Hospital, Parkville, VIC 3050, Australia*
[d] *Division of Cancer Medicine, Peter MacCallum Cancer Centre, East Melbourne, VIC 3002 Australia*
[e] *Department of Medical Oncology, Austin Health, Heidelberg, VIC 3084 Australia*
[f] *Medical Oncology Department, Queen Elizabeth Hospital and University of Adelaide, Woodville West, SA 5011 Australia*
[g] *Medical Oncology Department, Vall d'Hebron University Hospital, Universitat Autonoma de Barcelona, 08035 Barcelona, Spain*

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* Corresponding author. Tel.: +61 2 9926 5048; fax: +61 2 9926 5253.
E-mail address: stephen.clarke@sydney.edu.au (S.J. Clarke).

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Abstract

During the last 20 years there have been major therapeutic developments in colorectal cancer (CRC) with the introduction of multiple novel therapeutic agents into routine clinical practice. This has improved survival in both the adjuvant and advanced disease settings. However, improvements have come with substantial increases in expense to the community and potential toxicity to the patient. There has been substantial research to identify tumour factors in CRC that predict treatment response and survival outcomes. This research has identified clinically useful predictive biomarkers to aid clinical decision making, such as the presence or absence of *KRAS* gene mutations which can determine the benefit of using epidermal growth factor receptor (EGFR) inhibiting antibodies. However, less attention has been paid to the identification and impact of predictive patient-derived factors such as age, gender and the presence of comorbid conditions or evidence of a systemic inflammatory response. In this article, the current concepts of tumour and patient-related predictive factors in CRC management are reviewed.

Keywords: Colorectal cancer; Biomarkers; Tumour factors; Patient factors; Predictive; Prognostic

1. Introduction

Colorectal cancer (CRC) is the third most common epithelial malignancy in the world [1]. It is one of the leading causes of cancer mortality worldwide, accounting for greater than 10% of all cancer mortalities, with approximately 40–50% of all patients experiencing metastasis [1,2]. Major advances in the treatment of metastatic CRC (mCRC) over the last 20 years have significantly improved overall survival (OS) rates for mCRC patients from a median of 10 months to more than 20 months [3]. Improved surgical and staging techniques, the introduction of multiple new therapeutic agents (including oxaliplatin, irinotecan, capecitabine) and the availability of molecularly targeted therapies (such as bevacizumab, cetuximab, panitumumab, aflibercept and regorafenib) have significantly contributed to improved patient outcomes [4]. However, improvements in survival have come with substantial increases in cost to the community and toxicity to the individual. Thus the appropriate selection of patients for specific treatment is ever more important. Predictive and prognostic biomarkers have, and will continue to, facilitate the selection of suitable patients and the personalisation of treatment for mCRC.

Prognostic biomarkers identify patients with different disease outcomes regardless of treatment and may provide specific insights into their disease biology. Predictive biomarkers help to identify patients who are most likely to benefit, or not, from a specific treatment and can assist in guiding therapeutic decisions [5]. Substantial research has been conducted to identify predictive tumour factors that can indicate treatment response outcomes and survival endpoints. This research has largely focused on the presence or absence of genetic changes leading to a loss or gain of function, including *KRAS* mutations, a negative predictive marker for the use of the epidermal growth factor receptor (EGFR) inhibiting antibodies, and microsatellite instability (MSI) which is useful when considering the benefit of adjuvant chemotherapy in early stage colon cancer [6,7].

Tumour-related factors remain the central focus of predictive biomarker research. Patient-related factors have received less attention; however, they may also predict response to treatment and impact prognosis. Patient-related factors can have a marked influence upon the incidence of toxicities and may impact tolerance and compliance with therapy. Patient factors, such as age, gender, presence of comorbid conditions or evidence of a systemic inflammatory response, may be equally important as tumour factors in predicting response to mCRC treatment.

This review highlights the important advances made in the personalised treatment of mCRC and will discuss potential novel markers for improved selection of patients in the future. It carefully examines the robust evidence from clinical trials and evaluates how this may influence routine clinical practice.

2. Current approaches to the treatment of mCRC

With the availability of novel therapeutic agents for the treatment of mCRC, the selection of the most appropriate therapy is becoming increasingly important. Evidence-based medicine has provided insights into the most efficacious agents and treatment strategies, formulated from the results of randomised controlled trials and meta-analyses of these studies. However, it is essential to consider how evidence-based medicine translates to routine clinical practice. The outcomes of clinical trials may not apply to clinical practice due to differences in patient selection or the quality of treatment received [8]. It is also important to note that end-point data from clinical trials often do not match the treatment goals