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Review

Improving outcomes in colorectal cancer: Where do we go from here?

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Abstract Colorectal cancer (CRC) places a considerable burden on individuals and society in Europe, being the second most common cause of cancer-related death in the region. While earlier diagnosis and advances in treatment have considerably improved survival in recent years, further progress is needed. One of the greatest challenges associated with the treatment of CRC is the fact that current therapies for advanced disease are not curative, necessitating treatment for many years and placing a significant healthcare burden on society. To reduce the burden of CRC, care delivery must be more efficient and cost-effective. In particular, development of adequate screening programmes is needed, along with chemo-preventative strategies and newer, more active therapies. Further challenges include the lack of optimal selection of patients for adjuvant therapy, identification of the most appropriate target populations for current treatments and the optimum sequence for new molecular targeted agents. This article outlines current developments and unmet needs in CRC, and provides a detailed vision for improvements in the management of the disease. Implementation of some of these strategies will go some way to improving outcomes for patients with CRC.

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1. Introduction

Cancer places a considerable burden on society, being responsible for 29% of male and 23% of female deaths in Europe in 2008, and 7.6 million deaths globally.[1] Against this backdrop, the American Society of Clinical Oncology (ASCO) has developed a blueprint for action in an effort to accelerate progress in oncology.[2] The blueprint calls for a new approach to therapeutic development, employing molecularly-driven clinical trials leading to a more cost-effective process. While many of the proposals outlined in ASCO's vision are applicable to Europe, the region faces a number of unique challenges requiring a Europe-focussed approach. This article, focussing on unmet needs in colorectal cancer (CRC), forms the first in a series of reviews outlining current requirements in oncology and proposing future directions in a 'European call to action' across the healthcare community.

2. The healthcare burden and the challenges of CRC

CRC has a considerable impact on patients and healthcare systems in developed countries, and is the second most common cause of cancer-related death in Europe.[3,4] Around 25% of patients present with metastatic disease that significantly impacts on prognosis.[5] For those with localised CRC (Tumour, Nodes, Metastasis [TNM] stages I and II) the 5-year survival rate is as high as 93%, declining to 60%, 42% and 25% for patients with TNM stages IIIA, IIIB and IIIC, respectively. However, most patients with metastatic CRC (mCRC; stage IV) are not curable, with the 5-year survival rate falling to less than 10%.[6,7]

While early diagnosis of CRC in recent years combined with advances in treatment has considerably improved survival,[4] management of the disease remains challenging and further progress is needed. One problem associated with treatment is the heterogeneity of the CRC population.[8] In addition, as current therapies for advanced CRC are not curative, patients require treatment for many years, placing a significant healthcare burden on society. For this reason, development of adequate screening programmes is needed, along with chemo-preventative strategies and newer, more active therapies. Additional challenges include the lack of optimal selection of patients for adjuvant therapy, identification of the most appropriate target populations for current treatments and the optimum sequence for new molecular targeted agents.

3. Identifying new pathways in CRC through improved understanding of pathogenesis

An understanding of the genetics of inherited CRCs is important in order to identify at-risk individuals and improve diagnostic and therapeutic approaches. Familial predisposition is responsible for approximately one-quarter of CRCs, though hereditary syndromes with a known genetic defect are responsible for <5% of patients with CRC (Table 1).[8–14]

Three key pathways of genetic instability have been identified in CRC: chromosomal instability, microsatellite instability and CpG island methylator phenotype (CIMP), the methylator pathway.[14] These pathways are responsible for both sporadic and inherited cases, the most prevalent of which is Lynch syndrome, accounting for 2–4% of CRCs.[8] Other common syndromes include familial adenomatous polyposis (FAP) and serrated polyposis, a recently identified disease affecting 1 in 3000 individuals undergoing CRC screening.[15] While screening and surveillance strategies are now available for most inherited CRC syndromes, treatments for primary or secondary chemoprevention are lacking and new agents are needed, particularly for early-onset syndromes such as FAP and Lynch syndrome.

The identification of relevant molecular targets for cancer initiation and/or progression is an important focus for the development of targeted therapies in CRC and significant advances have been made recently as a result of projects such as the National Cancer Institute's Cancer Genome Atlas Network.[16] Patients whose tumours depend on particular targets can then be selected to avoid or minimise primary resistance to therapy. Mutations in the adenomatous polyposis coli (*APC*) and *KRAS* genes are thought to be among the earliest events in colorectal tumorigenesis.[17] *APC* mutation occurs through aberrant activation of the Wnt/β-catenin signalling pathway, with mutations within this pathway being responsible for around 90% of sporadic colon cancers.[18] *APC* is also the gene responsible for FAP and is a key target for intracellular signalling. A further important molecular target is epidermal growth factor receptor (EGFR), since around 10% of CRC tumours and 20–30% of *KRAS* wild-type tumours are dependent on the EGFR pathway.[19] EGFR activates multiple signalling pathways, including RAS/RAF/MEK/ERK and PTEN/PI3K/Akt (Fig. 1).[20,21] RAS/RAF/MEK/ERK is the main pathway upregulated when EGFR is activated,[21] though upregulated genes differ between tumour types, underlining the need for gene profiling for all CRC tumours.

4. Improving survival through advancements in CRC prevention and diagnosis

Effective screening to detect precursor lesions and early CRC is critical to reduce the burden of the disease on the healthcare system. Identification of adenomas before the development of carcinoma not only improves survival but also reduces cancer incidence. Indeed, the utility of this strategy has been accepted by the European Commission, which encourages the implementation of screening programmes throughout Europe.[22,23]

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