European Journal of Cancer (2014) **50**, 40–49

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Review

A systematic review of cost-effectiveness of monoclonal antibodies for metastatic colorectal cancer

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Available online 4 September 2013

KEYWORDS
Advanced colorectal cancer
Metastatic colorectal cancer
Monoclonal antibody
Bevacizumab
Cetuximab
Panitumumab
Targeted therapy
Health economics
Cost-effectiveness analysis
Cost-utility analysis

Abstract Metastatic colorectal cancer (mCRC) imposes a substantial health burden on patients and society. In recent years, advances in the treatment of mCRC have mainly resulted from the introduction of monoclonal antibodies (MoAbs). However, the application of these MoAbs considerably increases treatment costs. The objective of this article is to review and assess the economic evidence of MoAB treatment in mCRC. A systematic literature review was conducted and cost-effectiveness (CE) as well as cost-utility-studies were identified. For this, Medline, Embase, SciSearch, Cochrane, and nine other databases were searched from 2000 through February 2013 for full-text publications. The quality of the studies was assessed via a validated assessment tool (Quality of Health Economic Studies (QHES)). A total of 843 publications were screened. Of those, 15 studies involving the MoAbs bevacizumab, cetuximab and panitumumab met all inclusion criteria. Four studies analysed the CE of first-line treatment with bevacizumab and nine the CE of cetuximab in subsequent treatment lines. Two studies dealt with the CE of panitumumab. The analysis of sequential regimes and the direct comparison of two MoABs were analysed by only one study each. The quality of the included studies was high with the exception of one study.

Conclusions: The treatment with bevacizumab, cetuximab and panitumumab is mainly considered to be not cost-effective in patients with mCRC. However, testing for Kirsten ras oncogene (KRAS) mutation prior to the treatment with cetuximab or panitumumab is found to be clearly cost-effective compared to no testing. Future research should focus on the CE of first-line treatment with cetuximab or panitumumab and studies on upcoming agents like regorafenib and aflibercept.

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http://dx.doi.org/10.1016/j.ejca.2013.08.008

1. Introduction

Colorectal cancer (CRC) is one of the most common cancers (about 1.2 million cases worldwide in 2008) [1]. It is expected that the incidence of CRC will increase due to the demographic developments and lifestyles in the Western world.

The most important prognostic factor of CRC is the disease stage at the time of diagnosis. Approximately 25% of newly diagnosed patients have already developed metastases; almost 50% of all CRC patients will form metastases over time as the disease progresses [2]. Metastatic colorectal cancer (mCRC) is characterised by a high mortality rate. Palliative treatment with 5-fluorouracil (FU) and leucovorin (LV) was the best available treatment for many years. In the last decade increased surgical resections of metastasis as well as the development of new chemotherapies, like oxaliplatin or irinotecan, have improved overall survival [3].

More recently, advances in the treatment of mCRC have resulted mainly from the introduction of monoclonal antibodies as additional first-line treatment to chemotherapy or in subsequent treatment lines. These targeting agents aim to inhibit the tumour growth by interfering with specific proteins involved in tumour growth and progression (cell signalling), e.g. by blocking the signal transduction through vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR).

Currently widely-used monoclonal antibodies for the treatment of mCRC are the VEGF-antibody bevacizumab and the EGFR-antibodies cetuximab and panitumumab [4]. Moreover the anti-VEGF antibodies Regorafenib and Aflibercept were approved for the treatment of patients with mCRC by the US Food and Drug Administration (FDA) in late 2012 but still seek for an approval by the European Medicines Agency (EMA) [5,6]. In contrast to bevacizumab, cetuximab and panitumumab are only approved for a treatment of the subgroup of patients with Kirsten ras oncogene (KRAS) wild-type tumours. Hence, a biomarker test to detect the KRAS genotype of tumours and therefore a stratification of patients is mandatory prior to treatment with these EGFR-agents.

The application of these monoclonal antibodies in the mCRC treatment considerably increases treatment costs. Hence, it is necessary to assess the economic impact of the use of these agents. Moreover, health economic evaluations are necessary to support price negotiations as well as reimbursement decisions.

There exist several kinds of study designs for health economic evaluations. The most important are cost effectiveness analysis (CEA) and cost utility analysis (CUA). Thereby, the wording depends on the benefit measure which is used in health economic evaluations. Life-years gained (LYG) and quality-adjusted life-years (QALY), which is an index value combining gained additional life-time with quality of life during this time period, are the most frequently used benefit measures. Using QALY as the measure of consequence in a health economic evaluation is referred to as CUA; if other benefit measures like LYG are used, the evaluation is called CEA [7].

The main idea of health economic evaluations like CEA and CUA is to compare differences in costs to differences in health effects between alternative interventions [7]. The incremental approach is a common factor in all economic evaluations: they divide the additional costs of alternative A versus alternative B by the additional benefit of alternative A versus alternative B, resulting in the incremental cost-effectiveness ratio (ICER). It reflects the costs per additional benefit parameter (e.g. LYG, QALYs) which shall be incurred in the case of implementing alternative A in routine care. With these calculations, CEA und CUA aim at supporting the decision process regarding pricing and reimbursement of new technologies in health care systems. The objective of this article is to review and assess the economic evidence of monoclonal antibody treatment in mCRC. A systematic literature review was conducted and CEA- as well as CUA-studies were identified and analysed. The quality of the studies was assessed via a validated assessment tool.

2. Method

Prior to the systematic literature research, PICO (population, intervention, controll, outcome) elements were defined according to the objective of this review and presented in Table 1.

A systematic literature search in AMED, BIOSIS Previews, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, DAHTA-Database, Database of Abstracts of Reviews of Effects, EMBASE, EMBASE Alert, Health Technology Assessment Database, MEDLINE, NHS Economic Evaluation Database, SciSearch and SOMED database was conducted in September 2012 using the meta-database of the German Institute of Medical Documentation and Information (DIMDI) [8]. The search process was repeated in February 2013 in order to keep the review up to date. The full-text search included publications published in English and German during 2000–2012. The following German and English search terms were used and finally combined with AND: (i) (Darmkrebs OR Rektumkrebs OR mCRC OR CRC OR [{colorectal? OR kolorektal? OR colon OR kolon OR Rectum OR Bowel} AND {Cancer OR Carcinom? OR Karzinom OR Tumour OR Tumour OR Neoplasm?}]); (ii) (stadium III OR stadium IV OR stadium 3 OR stadium 4 OR stage III OR stage IV OR stage 3 OR stage 4 OR metasta? OR advanced); (iii) (cetuximab OR panitumumab OR bevacizumab OR Regorafenib OR Aflibercept); (iv) (Cost