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Original Research

First-line mFOLFOX plus cetuximab followed by mFOLFOX plus cetuximab or single-agent cetuximab as maintenance therapy in patients with metastatic colorectal cancer: Phase II randomised MACRO2 TTD study

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Abstract ***Background:*** This multicentre, randomised, and phase II study evaluated mFOLFOX+cetuximab followed by maintenance mFOLFOX+cetuximab or single-agent cetuximab in metastatic colorectal cancer (mCRC) patients (NCT01161316).

Patients and methods: Previously, untreated mCRC patients (wild-type *KRAS*) were randomised to receive cetuximab+mFOLFOX-6 (8 cycles for 2 weeks) followed by maintenance therapy: single-agent cetuximab (Arm-A) or mFOLFOX-6 + cetuximab (Arm-B) until progression. Primary endpoint was progression-free survival (PFS) at 9 months.

Results: One hundred ninety-three patients (median [range] age 60 [33−74] years) were randomised (2:1): 129 Arm-A versus 64 Arm-B. PFS at 9 months (95% confidence interval) showed non-inferiority between arms (Arm-A/Arm-B: 60 [52, 69]%/72 [61, 83]%, p [non-inferiority]< 0.1). There were no statistically significant differences in the PFS (Arm-A/Arm-B: 9 [95% CI 7, 10] months/10 [7,13] months, hazard ratio [HR] = 1.19 [0.80, 1.79]) or overall survival (23 [19, 28] months/27 [18, 36] months, HR = 1.24 [0.85, 1.79]) between arms. The objective response rate was also similar (48 [39, 57]%/39 [27, 52]%). The safety profile was similar between arms, and all patients experienced at least one adverse event (AE) (Arm-A/Arm-B grade ≥III AEs: 70%/68%). The most common grade ≥III AEs were as follows: neutropenia (Arm-A/Arm-B: 28%/26%), rash acneiform (15%/24%) and sensory neuropathy (2%/15%) in any group. Arm-A was associated with less grade ≥III rash and sensory neuropathy and a lower rate of serious AEs (20%/27%).

Conclusion(s): This phase II exploratory trial with a non-inferiority design suggests that maintenance therapy with single-agent cetuximab following mFOLFOX+cetuximab induction could be a valuable option compared with mFOLFOX+cetuximab treatment continuation. We await phase III trials to confirm single-agent cetuximab as maintenance therapy in mCRC patients.

1. Introduction

Colorectal cancer (CRC) is the third most common form of cancer and accounts for an estimated 694,000 deaths annually [1]; around one-quarter of all patients will present metastatic disease, and approximately half will go on to develop metastases [2]. Metastatic CRC (mCRC) is treated with a combination of cytotoxic drugs and targeted agents [3,4].

Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR) was initially approved for KRAS wild-type (WT) mCRC in patients who failed oxaliplatin and irinotecan-based therapy or were intolerant to irinotecan [5]. However, emerging data of *RAS* mutations as negative predictors of EGFR-targeting antibodies further refined the EMA approval (2009) to *RAS* WT (*KRAS* [exons 2 and 3] and *NRAS* [exons 2, 3, and 4] WT) mCRC patients. Recommending cetuximab as a first-line treatment in *RAS* WT mCRC patients together with anticancer chemotherapy treatments (irinotecan or oxaliplatin) in treatment naïve patients and as a single-agent in oxaliplatin and irinotecan treatment-refractory patients.

However, patients treated with oxaliplatin- or irinotecan-based therapies tend to discontinue treatment prematurely either due to severe neurotoxicity (oxaliplatin) or chronic diarrhoea (irinotecan) [6]. Non−chemotherapy-based maintenance therapy following first-line chemotherapy is a valuable and growing strategy used to decrease toxicity while maintaining efficacy. A number of maintenance therapy approaches have been evaluated, including intermittent schedules, chemotherapy holidays and single-agent regimens [7−17].

The MACRO2 trial seeks to optimise treatment with oxaliplatin-based regimens with the aim of preventing premature discontinuations for reasons other than

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