Critical Reviews in Oncology / Hematology 118 (2017) 54–62

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

Triplet (FOLFOXIRI) versus doublet (FOLFOX or FOLFIRI) backbone chemotherapy as first-line treatment of metastatic colorectal cancer: A systematic review and meta-analysis

Rui Pedro Marques[a,b,*], Gonçalo S. Duarte[c,d,e], Carmelo Sterrantino[f,g], Helena Luna Pais[b], António Quintela[b], Ana Paula Martins[a], João Costa[c,d,e]

[a] Research Institute of Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal
[b] Centro Hospitalar Lisboa Norte – Hospital de Santa Maria, Lisbon, Portugal
[c] Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal
[d] Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisboa, Portugal
[e] Centro de Estudos de Medicina Baseada na Evidência, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal
[f] Centre for Reviews and Dissemination, University of York, York, United Kingdom
[g] Department of Clinical and Experimental Medicine, Policlinico "G. Martino", University of Messina, Messina, Italy

ARTICLE INFO

Keywords:
Metastatic colorectal cancer
Triplet chemotherapy
FOLFOXIRI
Doublet chemotherapy
FOLFOX
FOLFIRI

ABSTRACT

Uncertainty exists regarding the comparative effectiveness of triplet chemotherapy (FOLFOXIRI) as backbone first-line chemotherapy for metastatic colorectal cancer (mCRC). We conducted a systematic review and meta-analysis of randomized-controlled trials (RCTs) comparing triplet versus doublet chemotherapy (FOLFOX or FOLFIRI) as first-line therapy in mCRC. Methods and reporting followed PRISMA and SAMPL guidelines.

Eight RCTs were included, comprising 1732 patients. In pooled analysis, FOLFOXIRI was associated with improvements in efficacy outcomes, notably with a 25% survival increase (95%CI: 10–37%). FOLFOXIRI was also associated with increased toxicity, with a non-significant 25% increase in the risk of patients experiencing grade ≥3 adverse events (95% CI: −3 to 61%) and with a 1.83 (95% CI: 1.62–2.07) increase in the rate ratio of grade ≥3 adverse events.

Moderate quality evidence suggests that first-line FOLFOXIRI provides clinically meaningful efficacy benefits in this setting, at the expense of increased toxicity. Further research is warranted to better characterize safety and to evaluate the most beneficial combination with targeted agents.

1. Introduction

The backbone of first-line chemotherapy for metastatic colorectal cancer (mCRC) consists of a fluoropyrimidine (FP) [intravenous (IV) 5-fluorouracil (5-FU) or the oral FP capecitabine] in various combinations and schedules. (Haller et al., 2005; Twelves et al., 2005; Tournigand et al., 2004; Sargent et al., 2011) Current guidelines advocate the combinations with oxaliplatin- (FOLFOX, fluorouracil, leucovorin, oxaliplatin or XELOX, capecitabine plus oxaliplatin) or irinotecan- (FOLFIRI, fluorouracil, leucovorin, irinotecan) based regimens (Van Cutsem et al., 2016; National Comprehensive Cancer Network, 2016). These regimens were shown to be superior to 5-FU + FA (Folinic Acid) alone. (Douillard et al., 2000; Andre et al., 2009)

Targeted therapy, with monoclonal antibodies binding to either the epidermal growth factor receptor (EGFR), or the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, is currently considered to be standard of care for first-line treatment of mCRC (Nordlinger et al., 2009). Clinical guidelines (Van Cutsem et al., 2016; National Comprehensive Cancer Network, 2016) recommend their selective addition to the previously mentioned chemotherapy regimens, taking into account patient's RAS status.

In recent years, new data have emerged on the use of triplet chemotherapy with 5-FU, oxaliplatin and irinotecan, named FOLFOXIRI, as backbone, in combination with targeted agents (Masi et al., 2010; Loupakis et al., 2014a; Assenat et al., 2011; Fornaro et al., 2013). Overall results showed an increased anti-tumoral activity although at the expense of greater toxicity. Thus, uncertainty remains concerning its clinical benefit, assessed in previous studies (Falcone et al., 2007; Souglakos et al., 2006). In fact, several trials are currently ongoing to further evaluate the benefit of triplet chemotherapy plus biologic agents

* Corresponding author at: Research Institute of Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Avenida Professor Gama Pinto, 1649-003 Lisboa, Portugal.
E-mail address: rui.p.marques@chln.min-saude.pt (R.P. Marques).

http://dx.doi.org/10.1016/j.critrevonc.2017.08.006
Received 30 October 2016; Received in revised form 4 May 2017; Accepted 19 August 2017

as first-line therapy in mCRC (Cremolini et al., 2015a). It is therefore relevant to compare the efficacy, safety and tolerability profiles of triplet chemotherapy (FOLFOXIRI) versus doublet chemotherapy (FOLFOX or FOLFIRI) as first-line therapy for unresectable mCRC.

2. Methods

The study protocol was published at PROSPERO (CRD42016035940). Methods and reporting of this systematic review followed PRISMA (Liberati et al., 2009) and SAMPL (Lang and Altman, 2015) guidelines.

2.1. Data sources and searches

Electronic identification of reports was conducted in Cochrane CENTRAL, MEDLINE, EMBASE, LILACS and clinical trial registries (International Clinical Trials Registry Platform of WHO and Clinicaltrials.gov). The last electronic search was in January 2017. We further cross-checked the references of potentially eligible randomized controlled trials (RCTs).

For the search strategy we combined the terms (colorectal neoplasm) with (FOLFOXIRI OR FOLFOX OR FOLFIRI). BMJ Clinical Evidence search filter was used to identify RCTs (see supplementary material for detailed search strategy).

2.2. Study selection

We included RCTs reporting on the efficacy, safety and tolerability comparing first-line FOLFOXIRI with FOLFOX/FOLFIRI in people of any age with unresectable mCRC. Studies comparing these backbone chemotherapy regimens in association with targeted agents were included unless the additional drug was administered only in one arm. We did not exclude studies a priori owing to poor quality, language, or time restrictions. Observational, non-controlled, or non-randomized interventional studies were excluded.

Three reviewers (RM, CS, HP) independently screened the titles and abstracts of retrieved reports for potential eligibility. They then screened the full text of potentially relevant trials.

2.3. Data collection process

Three reviewers (RM, CS, HP) independently extracted data from the included RCTs using a standardized electronic form. A further reviewer (JC) double-checked the extracted data. When possible we used data from intention-to-treat (ITT) populations. When such data were not available, we used data from modified ITT populations, defined as participants who were included and completed the study regardless of compliance with the allocated interventions. We extracted per protocol data only when data from ITT or modified ITT populations were unavailable.

All disagreements were solved by consensus or with the help of a fourth reviewer (GSD).

2.4. Outcomes and prioritization

Primary efficacy outcome was overall survival (OS), defined as the period of time (in months) between the date of first cycle of study chemotherapy and the date of patient death or last follow-up, whichever comes first. Primary safety outcome was the proportion of participants with grade ≥ 3 adverse events (AE), as defined by the Common Terminology Criteria for Adverse Events (CTCAE).

Secondary efficacy outcomes were: progression-free survival (PFS), defined as the period of time (in months) between the date of first cycle of study chemotherapy and the date of first tumor progression (according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria), patient death or last follow-up, whichever comes first; overall response rate (ORR), measured in proportion of patients presenting a complete response (CR) or a partial response (PR) as best response, according to RECIST criteria, with CR and PR rates also considered separately where available; rate of metastasis resection, measured as the percentage of participants receiving metastasis resection with curative intent or complete remission (R0 resection); R1 (to microscopic residual tumor) and R2 (to macroscopic residual tumor) resection data; and health-related quality of life (HRQoL), as measured through any validated instrument. Secondary safety outcomes were: relative difference between rate of adverse events in each treatment arm (rate ratio) reported through the trial; proportion of patients with any AE; and proportion of patients with AEs of special interest. Tolerability was evaluated by means of the participant withdrawal rate (overall and due to AEs) after study enrolment.

2.5. Assessment of study quality

Three reviewers (CS, HP, RM) independently assessed the risk of bias of individual studies using the Cochrane risk of bias tool (Higgins, 2011), using information from the published report. We added two domains: risk of 'for-profit bias' and 'other bias'. The overall risk of bias assessment for each trial was divided as high and low risk, with high risk being those trials in which at least one domain was assessed as having a high risk of bias.

2.6. Statistical methods

Statistical analyses were performed using Review Manager version 5.3 (Review Manager, 2014).

We pooled effect measures using a random-effects model for dichotomous outcomes, and the generalized inverse-variance method for continuous outcomes (Higgins, 2011), and derived hazard ratios (HR) or risk ratios (RR).

We used relative measurements because these measures of association, such as RR, are more similar across studies with different designs, populations, and lengths of follow-up than absolute measurements of treatment effect (Deeks, 2002). However, when we found statistically significant differences between the treatment groups, we further determined absolute effects and derived the number needed to treat (NNT) with FOLFOXIRI for an additional patient to experience benefit (NNTB) or harm (NNTH), taking into account the baseline risk (weighted proportion of event rate in the control group), because of the differences in the predicted absolute effect of treatment according to variation in baseline risk between groups (Deeks, 2002). We presented all results with a 95% confidence interval (95% CI). We assessed heterogeneity with the Cochran Q test and the I^2 test (Higgins et al., 2011).

Publication bias was assessed through visual inspection of funnel plots (if at least 10 studies were included) (Higgins, 2011) and with Egger's (Egger et al., 1997) regression test.

We conducted 4 pre-planned subgroup analyses, according to the: 1) administration or not of concomitant targeted therapies; 2) metastatic site; 3) study phase (phase II or III); and 4) the use of FOLFOX or FOLFIRI as comparator. Differences between subgroups were assessed based on random effects model due to the lower risk of false-positive results (Higgins and Thompson, 2004). Pre-planned sensitivity analyses were also conducted by repeating primary analyses after excluding trials that used non-standard chemotherapy regimens.

2.7. Confidence in cumulative evidence

We evaluated the overall quality of evidence (also called confidence in the evidence) using the grading of recommendations assessment, development and evaluation (GRADE) working group methods (Schünemann et al., 2011).