Critical Reviews in Oncology / Hematology 122 (2018) 21–29

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

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

A systematic review of the safety profile of the different combinations of fluoropyrimidines and oxaliplatin in the treatment of colorectal cancer patients

Chiara Baratelli[a], Clizia Zichi[b], Massimo Di Maio[a,*], Maria Pia Brizzi[b], Cristina Sonetto[b], Giorgio Vittorio Scagliotti[b], Marco Tampellini[b]

[a] Department of Oncology, Mauriziano Umberto I Hospital, Largo Turati 62, Torino, Italy
[b] Department of Oncology, AOU San Luigi Gonzaga, Regione Gonzole 10, Orbassano, Italy

ARTICLE INFO

Keywords:
Colorectal cancer
Oxaliplatin
Capecitabine
5-fluorouracil
Safety profile
Tolerability

ABSTRACT

The available fluoropyrimidines and oxaliplatin combinations for colorectal cancer patients have different safety profiles. The aim of this systematic review was to compare their toxicities.

The eligible studies were classified as: no bolus; 5-FU single bolus; 5-FU double bolus; capecitabine. We calculated the incidence of "any-grade" and "severe" toxicity for haematological and non-haematological adverse events of each group.

We identified 184 treatment groups; compared to 5-FU double bolus, except for high-grade anaemia, all the groups showed reduced risk of haematological toxicities, with the most relevant advantages for single bolus regimens. Concerning non-haematological toxicities, compared to double bolus, the single bolus group showed a statistically significant reduced risk for many gastrointestinal toxicities and for pheripheral neuropathy.

This is the first systematic review of the toxicity profile of different 5-FU or capecitabine and oxaliplatin regimens. Single 5-FU bolus is associated with a definitely favourable toxicity profile, both for haematological and non-haematological toxicity.

1. Introduction

Colorectal cancer represents the second most frequent malignancy in men and the third in women worldwide, with an incidence of 9.7 cases per 100,000 people per year; it is responsible of 8.5% of all cancer-related deaths (Ferlay et al., 2015).

In the last decade, the introduction of new drugs, especially the anti-vascular endothelial growth factor (VEGF) and anti-epidermal growth factor receptor (EGFR) targeted agents, has prolonged the life expectancy of patients affected by metastatic colorectal cancer (mCRC). Nevertheless, chemotherapy remains the backbone of anticancer treatment in this setting.

Beside 5-fluorouracil (5-FU), the main compound at the basis of mCRC treatment (Advanced Colorectal Cancer Meta-Analysis Project, 1992; Thirion et al., 2004), several prodrugs have been developed. One of them, capecitabine, has demonstrated similar efficacy compared to 5-FU, with a slightly different safety profile (Cassidy et al., 2004; Diaz-Rubio et al., 2007; Cassidy et al., 2008). Both drugs are used as single agents, or as part of a regimen; oxaliplatin is one of the most frequently combined drugs. The main international guidelines (Van Cutsem et al., 2017; Anon, 2017a) recommend the association of 5-fluorouracil/leucovorin and oxaliplatin or capecitabine and oxaliplatin (± targeted agents) as first- or second-line regimen for mCRC patients. These combinations have indeed demonstrated an advantage in terms of progression free survival (PFS) and overall survival (OS) when compared to 5-FU alone in this setting. Similarly, 5-FU as monotherapy or part of a combination schedule represents the standard approach for patients with stage II and III colorectal cancer candidated to a post-surgical adjuvant treatment.

While the timing, dose and modality of administration of capecitabine and oxaliplatin (generally indicated as XELOX or, less frequently, CAPOX) are quite standardized, several schedules of FOLFOX have been introduced in clinical practice, including FOLFOX-2, FOLFOX-4, FOLFOX-6, FOLFOX-7, FUOX, FUFOX, their modified schedules and the chronomodulated regimens. These regimens basically differ in the administration of bolus 5-FU: two boli per cycle (FOLFOX-4), one bolus (FOLFOX-6), or none (FOLFOX-2 and FOLFOX-7).

FOLFOX-4, FOLFOX-6 and XELOX are currently considered equally

* Corresponding author at: Department of Oncology, University of Torino, Mauriziano Umberto I Hospital, Largo Turati, 62 10100 Torino, Italy.
E-mail address: massimo.dimaio@unito.it (M. Di Maio).

https://doi.org/10.1016/j.critrevonc.2017.12.010
Received 6 February 2017; Received in revised form 29 September 2017; Accepted 12 December 2017

active for CRC patients (Diaz-Rubio et al., 2007; Cassidy et al., 2008); nevertheless, as bolus and infusional 5-FU present different mechanisms of action, to the best of our knowledge no study has directly compared their safety profiles, in terms of both haematological and non-haematological adverse events. We consequently performed a systematic review of the currently available literature collecting toxicity data of the above mentioned combinations administered to colorectal cancer patients, in order to explore whether the different number of 5-FU boli might result in different tolerability profiles.

2. Materials and methods

2.1. Objective of the study

The primary objective of this study was to compare the toxicity profile of different FOLFOX or capecitabine and oxaliplatin regimens, according to the type of fluoropyrimidine and its modality of administration, in order to define to what extent this influenced the toxicity profile of the treatment.

2.2. Studies selection

We performed five separate systematic researches on PubMed database (Anon, 2017b), using the following keywords: “FOLFOX”; “FUOX”; “FUFOX”; “XELOX” and “CAPOX”. The search was completed and updated in March 2016: all the papers published up to 31st December 2015 were included. Only papers written in English were eligible for the analysis. We included all publications concerning colorectal cancer; independently from the stage of the disease; the setting of treatment (adjuvant; neo-adjuvant or palliative); the number and characteristics of previous lines of treatment. Consequently; we collected data coming from prospective trials (both randomized and non randomized) as well as retrospective studies and case series in which at least one of the previously mentioned regimens had been used.

2.3. Data collection

The data were collected by two independent investigators (C.B. and C.Z.) and then computed by three investigators (C.B., M.D.M. and M.T.). Eventual controversies were solved through discussion between the authors. The following parameters about each study were collected: name of the first author, year of publication, number of patients included in the study, for each of the treatment arms taken into account, name of the regimen of chemotherapy, line of treatment, dose of oxaliplatin and 5-fluorouracil or capecitabine, target agent(s) associated, schedule of administration, details about incidence of haematological toxicity (anaemia, neutropenia, febrile neutropenia, thrombocytopenia) and non-haematological toxicity (nausea, vomiting, diarrhoea, oral mucositis, hand-foot syndrome, peripheral neuropathy, cardiotoxicity and liver toxicity). When available, data about nausea and vomiting were collected separately, with the exception of studies where both toxicities were described together as emesis.

2.4. Data elaboration

The eligible studies were classified according to the modality of administration of the fluopirimydine associated to oxaliplatin: (i) 5-FU double bolus (± continuous infusion); (ii) 5-FU single bolus (± continuous infusion); (iii) exclusive continuous infusion of 5-FU (without bolus); (iv) capecitabine. In addition, treatments were grouped according to the presence of an associated biological drug: (i) no additional drugs; (ii) “standard” anti-EGFR (cetuximab or panitumumab); (iii) “standard” anti-VEGF (bevacizumab or aflibercept); (iv) other experimental drugs.

For each toxicity included in the analysis, we calculated the incidence of “any grade” and “severe” (grade 3–4 according to Common Terminology Criteria for Adverse Events -CTCAE-) (U.S. Department of Health and Human Services, 2006; U.S. Department of Health and Human Services, 2010) toxicity. Analysis was performed on the whole number of studies included and for each of the subgroups.

In order to explore the role of potential confounding factors, we performed subgroup analyses according to the type of paper (considering only prospective studies, with the exclusion of retrospective analyses that could underestimate toxicity), to the intent of treatment (studies including patients in the adjuvant setting; studies including patients with advanced disease) and to the use of additional agents to the 5-FU/capecitabine and oxaliplatin regimen (studies with no added biological drug; studies with the addition of anti-EGFR; studies with the addition of anti-angiogenic agent).

2.5. Statistical analyses

The incidence of toxicities was obtained by summing the number of patients presenting a side effect divided by the sum of all the patients treated in the studies with available information about that toxicity.

We selected the 5-FU double bolus group as our referral regimen; we then performed a Chi-square test in order to express the risk of each toxicity as an odds ratio (OR) for each of the other groups (no bolus, single bolus, capecitabine) vs double bolus. A sensitivity analysis, with the same methods, was performed in prospective trials only, with the exclusion of retrospective analyses. To reduce the risk of false positive results related to multiple comparisons, we conservatively considered as statistically significant p values < 0.001. Subgroup analyses according to the treatment setting and to the type of added biological agent were performed with exploratory aim, without ststistical tests.

3. Results

Through the electronic search, last checked on 31st March 2016, we identified: 1473 citations for “FOLFOX”, 7 for “FUOX”, 13 for “FUFOX”, 349 for “XELOX” and 87 for “CAPOX”.

We initially performed a selection based on the title of the paper, then one selection based on the abstract, and a final selection based on the full text. At the end of the process, papers satisfying inclusion criteria for our study were: 84 concerning “FOLFOX”, 36 “XELOX”, 8 “CAPOX”, 2 “FUFOX” and 1 “FUOX”. XELOX and CAPOX were grouped as a single entity. Considering that some studies were designed in order to compare different treatments or schedules, the whole number of study arms or case series for each regimen analysed in this review were: 120 “FOLFOX”, 59 “XELOX/CAPOX”, 3 “FUFOX” and 2 “FUOX”.

As detailed in Fig. 1, the main reasons for exclusion of a paper were: ineligible type of paper (single case reports, meta-analyses, reviews, editorials); trials focused on treatment other than chemotherapy (surgery, radiotherapy, combined modalities, interventional radiology); type of tumour (other than colorectal); case mix of several regimens (e.g. FOLFOX + XELOX evaluated as a single entity, merged data of different FOLFOX schedules) without scattered data; preclinical studies; unavailability of full-text article; lack of side effect description; other reasons (publications focused on economical aspects, patients' compliance, concomitant diseases, quality of life).

The characteristics of each regimen included in the analysis, including the dose and schedule of 5-fluorouracil, capecitabine and oxaliplatin, the number of boluses and the interval between administrations are described below.

FOLFOX-4 is the only regimen with a double 5-FU bolus (total bolus dose: 800 mg/m^2), associated to 5-FU continuous infusion (1200 mg/m^2 over 46 h) and oxaliplatin 85 mg/m^2.

A single 5-FU bolus (400 mg/m^2) followed by a 46-h continuous infusion (2400 mg/m^2) characterizes both FOLFOX-6 (with oxliplatin 100 mg/m^2) and FOLFOX-7 (oxaliplatin 130 mg/m^2).

All the above described regimens, including one or more boluses, are administered every 2 weeks.