REVIEW ARTICLE

Oxaliplatin versus Irinotecan in advanced colorectal cancer

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ABSTRACT

Colorectal cancer is a highly prevalent and lethal neoplasm. The reason for this high number of deaths is the detection of the disease in metastatic stages, which are difficult to cure and require adjuvant or palliative chemotherapy therapy. Currently, the main chemotherapeutic treatment of this neoplasm is based on the drugs Oxaliplatin or Irinotecan, alone or combined with other drugs. The objective of this systematic review is to evaluate whether there is superiority of the chemotherapy regimen with Irinotecan over that with Oxaliplatin. Analysis of randomized clinical trials, phase II or III, was performed in the electronic databases Central and PubMed. Inclusion criteria: randomized clinical trials comparing irinotecan- or oxaliplatin-based regimens as first-line treatments for metastatic colorectal cancer. The primary endpoint analyzed was the superiority between chemotherapies on overall survival. Secondary endpoints included progression-free survival, response rate, and side effects. PROSPERO registration: CRD42019130339. There was no significant difference in the 13 studies on patient survival. On drug side effects, irinotecan-based regimens were associated with a high incidence of neutropenia and severe diarrhea. Those associated with oxaliplatin were associated with a high incidence of sensory neuropathy. There was no statistically significant difference in overall survival, progression-free survival, and response rate when comparing patients receiving oxaliplatin and irinotecan.

Keywords: Colorectal neoplasms, Irinotecan, Oxaliplatin.

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INTRODUCTION

Colorectal cancer is the second most common neoplasm in the Brazilian population, responsible for 18,867 deaths in 2017 in Brazil[1].In general, colorectal cancer is diagnosed from signs or symptoms that occur in locally advanced or metastatic stages, therefore with a reserved prognosis[2,3].

Chemotherapy is the main treatment for advanced colorectal cancer, in which oxaliplatin and/or irinotecan, associated or not with other chemotherapeutic agents, are used as the first line of treatment[4].

There is much controversy regarding the efficacy of oxaliplatin compared to irinotecan in advanced colorectal cancer as first-line chemotherapy treatment. This study aims to compare first-line chemotherapy protocols based on oxaliplatin versus those with irinotecan regarding overall survival, disease progression-free survival, response rate, and major side effects.

METHOD

Search strategy

The search was performed in the electronic databases Central Registry of Controlled Trials of the Cochrane Library (CENTRAL) and PubMed. The search was last updated on June 3, 2021. Inclusion criteria were as follows: randomized, phase II or III clinical trials comparing irinotecan- or oxaliplatin-based regimens as first-line treatments for metastatic colorectal cancer; no language or date limits were used. Ongoing studies that did not have sufficient data for analysis and non-randomized or phase I clinical trials were excluded. This review is registered in PROSPERO, with the following identification: CRD42019130339.

The terms used for the search included: (1) **Rectal (i.e.,** Rectum, Rectums), **Sigmoid (i.e.,** Sigmoid Colon, Sigmoidal), **Colonic (i.e.,** Colon), **Intestinal (i.e.,** Intestines), (2) **Neoplasms (i.e.,** Cancer, Cancers, Malignancies, Malignancy, Malignant, Neoplasia, Neoplasias, Neoplasm, Tumor, Tumors), (3) **Irinotecan (i.e.,** 7 Ethyl 10 hydroxycamptothecin, 7-Ethyl-10-hydroxycamptothecin, CPT 11, CPT-11, CPT11, Camptosar, Camptothecin 11, Camptothecin-11, Irinotecan Hydrochloride, Irrinotecan, NK012 Compound, SN 38, SN 38 11, SN-38, SN-38-11, SN3811), (4) **Oxaliplatin (i.e.,** Eloxatin, platinum-based chemotherapy drug, 1,2 Diaminocyclohexane Platinum Oxalate, 1,2 Diaminocyclohexane Platinum Oxalate, 1,2-Diamminocyclohexane(trans-1) oxolatoplatinum(II), ACT 078, ACT-078, ACT078, Cis-oxalato-(trans-l)-1,2-diaminocyclohexane-platinum(II), Eloxatine, L-OHP Cpd, Oxalato-(1,2-cyclohexanediamine)platinum II, Oxaliplatin, (SP-4-2-(1R-trans))-isomer. Oxaliplatin, (SP-4-2-(1S-trans))-isomer, Oxaliplatin, (SP-4-3-(cis))-isomer, Oxaliplatine, Platinum(II)-1,2-cyclohexanediamine Oxalate).

Selection of clinical trials

Clinical trials were selected by separate analysis of at least two of the three authors independently. The selection was made by first analyzing the title and then the abstracts, followed by reading the full text. Five hundred and twelve studies were found in the database search (n=379 PUBMED, n=133 CENTRAL). Of these, 96 were excluded for being duplicates. Four hundred and sixteen studies were analyzed based on their title and abstract, 49 studies were selected for full reading, 36 were excluded for ineligible drug combinations or mismatched outcomes, and finally, 13 studies were included in this systematic review (Figure 1).

Primary outcomes

Evaluate whether there is superiority between chemotherapies on overall survival.

Secondary outcomes

Assess disease progression-free survival, response rate, and major side effects.

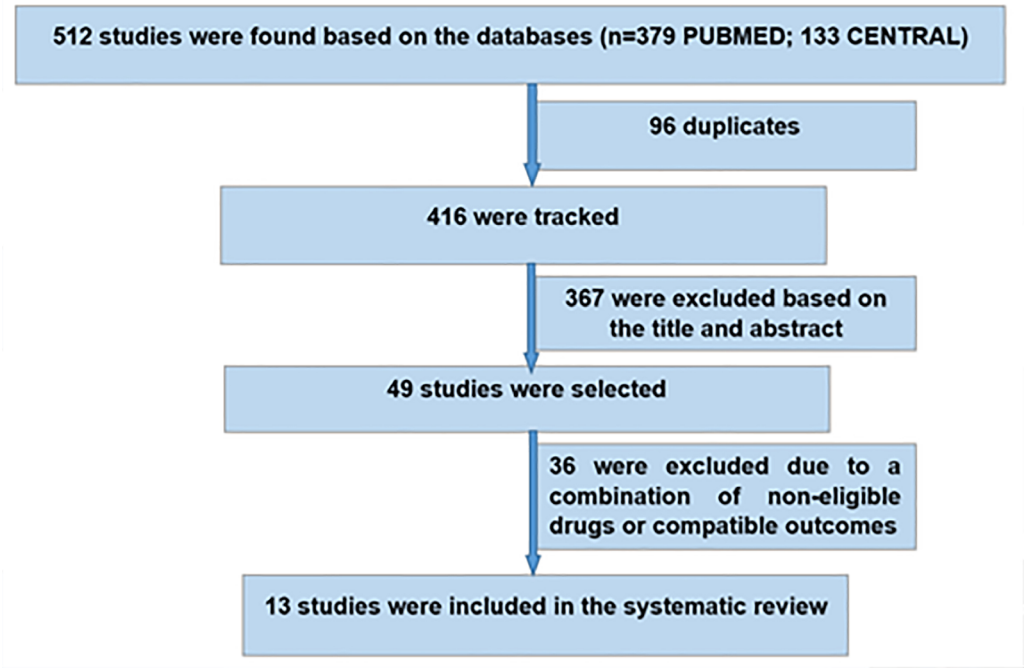

Figure 1: Study flow diagram.

RESULTS

A total of 2,660 patients with metastatic colon and rectal cancer were analyzed in 13 randomized, phase II or phase III clinical trials.

The therapies compared in all the studies had oxaliplatin or irinotecan in their composition, with CapOx or CapIRI being the combinations used in three of the clinical trials, OXAFAFU or IRIFAFU being the therapy in two studies, FOLFOX or FOLFIRI was used in six studies, five of which also added bevacizumab to the combination therapy, TEGAFOX or TEGAFIRI was used in one study, and Raltitrexed + oxaliplatin or CPT-11 was used in one study.

DISCUSSION

The systematic review found no scientific evidence that oxaliplatin therapy is superior to irinotecan therapy. However, the side effect profile found with oxaliplatin was different from that found with irinotecan.

In the study by Comella et al., better results in disease-free survival (p=0.046) and overall survival of patients (p=0.032) were identified in the group that received oxaliplatin when these patients were adequate to performance status, different from the results obtained for the survival of patients with low-performance status (p=0.058)[15]. The other studies had no statistically significant results regarding overall survival, disease progression-free survival, and efficacy between chemotherapy regimens based on oxaliplatin or irinotecan. As an example of what is discussed in this paragraph, the PLANET-TTD study, which analyzed colorectal cancer with alterations in WT-RAS and WT-KRAS genes, obtained as results the absence of significant difference in efficacy or safety between Pmab-FOLFOX4 and Pmab-FOLFIRI[9]. The toxic profile of the drugs was similar in the studies analyzed in this systematic review, yet the side effects were distinct. The oxaliplatin-based regimens had a higher incidence of sensory neuropathy; a demonstration of this statement was the study by Yamazaki et al. in which the adverse effect of sensory neuropathy of oxaliplatin led to discontinuation of treatment in some patients, unlike treatment with irinotecan, which did not present this adverse reaction and was tolerated throughout the treatment analyzed by the study[11].

In contrast, the most prevalent side effects of the irinotecan regimen were neutropenia and severe diarrhea. As an example, the study by Comella et al., observed a lower incidence of

Table 1

Characteristics of the studies included.

Authors	Year	Phase	Primary outcome	Secondary outcome	Intervention	N. of patients	Results
Schmiegel et al.[5]	2013	II	PFS	OS; TT; secondary resection of liver/lung metastases.	BEV + CapOx or mCapIri	255	Both CapOx-bevacizumab and mCapIri-bevacizumab show presented promising activity and an excellent toxic effect profile, with no significant difference when compared.
Feliu et al.[6]	2005	II	Efficacy	PFS and TT	Raltitrexed + oxaliplatin or CPT-11	94	Both schemes have high efficacy and their total toxicity levels are similar.
Nakayama et al.[7]	2018	III	ORR	PFS, OS and safety	BEV + CapOX or CapIRI	107	CapOX plus bevacizumab and CapIRI plus bevacizumab show no significant difference in efficacy and feasibility.
Parikh et al.[8]	2018	II	PFS	Efficacy and TT	FOLFOX6 + BEV or FOLFIRI + BEV	376	Both therapies have equivalent progression-free survival, efficacy and toxicity.
Carrato et al.[9]	2017	II	ORR	Liver metastases resection rate, PFS, OS, AE and perioperative safety.	Pmab + FOLFOX4 oR FOLFIRI	77	No significant difference in efficacy was observed between the two regimens. There was also no significant difference in secondary outcomes between the two therapies.
Folprecht et al.[10]	2014	II	ORR	OS, PFS	Cmab + FOLFOX6 or FOLFIRI	111	Therapies have equivalent efficacy.
Yamazaki et al.[11]	2016	III	PFS	RR, OS, QL	BEV + FOLFOX6 FOLFIRI	402	FOLFIRI + BEV was not inferior in progression-free survival compared with mFOLFOX6 + BEV.
Ocvirk et al.[12]	2010	II	PFS	ORR, PFS, OS and safety	Cmab + FOLFOX6 or FOLFIRI	181	Combinations of cetuximab with FOLFOX6 or FOLFIRI are equally effective.
Rosati et al.[13]	2010	II	ORR	OS, AE	CapOx or CapIRI	94	CAPOX and CAPIRI had similar efficacy in elderly patients over 75 years of age, although CAPOX appears to be better tolerated.
Bajetta et al.[14]	2007	II	AE	Efficacy	TEGAFOX or TEGAFIRI	141	TEGAFIRI and TEGAFOX are equally effective and tolerable first-line therapies
Comella et al.[15]	2005	III	ORR	FFS and OS	OXAFAFU or IRIFAFU	277	Improved patient PFS and OS outcomes in patients receiving OXIFAFU when matched to performance status.

Kalofonos et al.[16]	2005	II	ORR	CR, SD, PR.	LV + 5-FU + Oxiliplatin or IRinotecan	185	The therapies had equally substantial efficacies and manageable toxicity profiles in first-line treatment
Colucci et al.[17]	2005	III	ORR	OS, TTP	FOLFOX or FOLFIRI	360	No difference in ORR, TTP and OS for patients treated with the FOLFIRI or FOLFOX4 regimen.

Capecitabine/oxaliplatin (CapOx) plus bevacizumab and dose-modified capecitabine / irinotecan (mCapIri); bevacizumab (BEV), Progression-free survival (PFS); Panitumumab (Pmab); objective response rate (ORR); Toxicity rate (TT); response rate (RR); complete response (CR); progressive disease (PD); partial response (PR); Failure-free survival (FFS); time to progression (TTP); Adverse effects (AE); progression-free survival (PS); quality of life (QL); overall survival (OS); uracil/tegafur/leucovorin+irinotec (TEGAFIRI); uracil/tegafur/leucovorin+oxaliplatin (TEGAFOX); folic acid, 5-fluorouracil, oxaliplatin (FOLFOX); folic acid, 5- fluorouracil + irinotecan (FOLFIRI); Pmab (Panitumumumab); bevacizumab (BEV); cetuximab (Cmab); 5-fluorouracil (5-FU); Leucovorin (LV); Capecitabine+oxyglaplatin (CapOX); capecitabine+IRINOTECAN (CapIRI); levo-folinic acid (l-FA).

severe diarrhea in patients who used oxaliplatin in comparison to those who used irinotecan ($p=0.005$)[15]. In contrast to the other studies analyzed in this systematic review, the PLANET study found no significant difference in the frequency of severe diarrhea between the two chemotherapy regimens analyzed.

The other side effects analyzed in this systematic review were similar between the two chemotherapy regimens, with the following other adverse reactions: nausea, vomiting, neurotoxicity, acne from dermatitis, mucositis, skin rashes, anorexia, anemia, and asthenia.

CONCLUSION

The systematic review showed no scientific evidence of a difference in overall survival, efficacy, and progression-free survival between oxaliplatin- and irinotecan-based regimens. The side effect profile between irinotecan and oxaliplatin chemotherapy regimens were distinct, with the oxaliplatin regimen predominating sensitive neuropathy and the irinotecan regimen predominating neutropenia and severe diarrhea; however, the overall toxicity range was similar between the two therapies, both being safe and well tolerated.

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Conflict of interests
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