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Review

Second line with oxaliplatin- or irinotecan-based chemotherapy for gemcitabine-pretreated pancreatic cancer: A systematic review

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Abstract ***Background:*** oxaliplatin (OXA)- and irinotecan (IRI)-based chemotherapies are the most frequently used salvage regimens in patients with metastatic pancreatic cancer (PC) after first-line gemcitabine-based therapy. There are no prospective comparisons of these regimens in this setting. We conducted a systematic review of published trials to compare the efficacy of these treatments.
Methods: studies that enrolled patients with stage IV disease receiving chemotherapy with OXA or IRI plus fluoropyrimidines were identified using electronic databases (Pubmed, Embase, SCOPUS, CINAHL, Web of Science and Cochrane Library). Clinical outcomes were compared using weighted values of median overall survival (OS), progression-free survival (PFS), response rates (RRs), and clinical benefit rates (CBRs). A 2-tailed *t*-test with a significance level of 0.05 for comparisons of continuous variables and a Chi-squared test for comparisons of proportions were used.

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Results: overall, 24 studies were included. The pooled overall response rate (ORR), disease control rate (DCR), PFS and OS were 11%, 37.9%, 2.87 and 5.48 months respectively. There was no significant difference in response rates between OXA-based and IRI-based chemotherapies (11.9% versus 8.7%; Chi-squared P = 0.1), respectively. Also there was no significant difference in median PFS (2.9 months versus 2.7 months; *t*-test P = 0.72), OS (5.3 months versus 5.5 months; *t*-test P = 0.72), but a greater DCR with OXA-based chemotherapy (41.1% versus 29.4%; Chi-squared P = 0.0008).
Conclusion: OXA- and IRI-containing regimens were associated with similar efficacy when used after gemcitabine-based chemotherapy in patients with advanced pancreatic cancer.

1. Introduction

Pancreatic cancer (PC) represents a high-lethality malignancy, for which minimal improvement in the effectiveness of standard therapy for metastatic patients has been achieved over time. In particular, the benefit of salvage therapy is limited with only a modest overall survival (OS) gain compared to best supportive care [1]. The current standard of care as first-line chemotherapy is a combination of gemcitabine (GEM) with nab-paclitaxel or, for fit patients only, a multidrug polychemotherapy regimen called FOLFIRINOX, consisting of 5-fluorouracil (5-FU), Oxaliplatin (OXA) and irinotecan (IRI) [2,3]. At progression after GEM + nab-paclitaxel, a fluoropyrimidine (FP) alone or in combination with OXA or IRI (or nano liposomal IRI [NALIRI] an IRI free base encapsulated in liposome nanoparticles), are reasonable options as also suggested by American Society of Clinical Oncology (ASCO) guidelines [4]. However, there are no large randomised trials that answer the question of which is the best option between IRI- and OXA-containing regimens regarding efficacy and toxicity [15,28]. In general, due to the limited evidence derived from lack of head-to-head trials of the two regimens, a direct comparison is not possible and indirect network analyses are difficult to be carried out [5].

To provide more compelling evidence, we performed a review and a pooled analysis of published trials to compare OXA- versus IRI-based chemotherapy for GEM-pretreated PC patients.

2. Methods

A systematic search of the literature of electronic databases (Pubmed, Embase, SCOPUS, CINAHL, Web of Science and Cochrane Library) from inception to December 2016 for all published (prospective trials or retrospective case series) studies without date restriction was conducted using the terms ((‘irinotecan’ [Supplementary Concept] OR ‘irinotecan’ [All Fields]) OR (‘oxaliplatin’ [Supplementary Concept] OR ‘oxaliplatin’ [All Fields])) AND (second [All Fields] AND ‘line’ [All Fields]) AND (‘pancreatic cancer’ [All Fields] OR ‘pancreatic carcinoma’ [All Fields]) AND ((‘fluorouracil’ [MeSH Terms] OR ‘fluorouracil’ [All Fields] OR ‘5 fluorouracil’ [All Fields]) OR (‘capecitabine’ [MeSH Terms] OR ‘capecitabine’ [All Fields])) for the Pubmed searches. Relevant studies were also searched and retrieved from the conference proceedings of annual meetings of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) congresses.

3. Study eligibility

The studies were independently reviewed by 3 authors (FP, GT, and AI) for eligibility. Trials using FP-based chemotherapy with either OXA or IRI and published in English language were included in this analysis. Phase I trials and trials that enrolled fewer than 20 patients were excluded from the analysis. Trials with the addition of other therapeutic or experimental agents, except folinic acid, to the OXA or IRI + FP combinations, were not allowed for inclusion. For data that were both presented at a meeting and subsequently published in full form, only the data from the full publication was included. If data had been presented multiple times, then the most updated version was used, and the older data excluded. Studies were included if at least one of the outcome measures was extractable from the study.

4. Data extraction and statistical analysis

The extracted data included the type of study, number of patients, median age/performance status, previous chemotherapy, treatment, and clinical outcomes including overall response rate (ORR), progression-free survival (PFS) or time to progression (TTP), median OS and toxic effects. For trials investigating multiple treatment arms, data were only included from the arms that used an OXA-based or IRI-based chemotherapy. The outcome data extracted for each arm were analysed using random effect models and reported as weighted