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Original article

Systematic review and meta-analysis on targeted therapy in advanced pancreatic cancer

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ABSTRACT

Aim: A systematic review and meta-analysis from literature has been performed to assess the impact of targeted therapy in advanced pancreatic cancer.
Methods: By searching different literature databases and major cancer meetings proceedings, data from all randomized clinical trials designed to investigate molecular targeted agents in the treatment of advanced pancreatic cancer were collected. The time-frame between January 2007 and March 2015 was selected. Data on predefined end-points, including overall survival, progression-free survival in terms of Hazard Ratio and response-rate were extracted and analyzed by a random effects model. Pooled data analysis was performed according to the DerSimonian and Laird test. The occurrence of publication bias was investigated through Begg's test by visual inspection of funnel plots.
Results: Twenty-seven randomized clinical trials for a total of 8205 patients were selected and included in the final analysis. A significant benefit was demonstrated for anti-EGFR agents on overall survival (HR = 0.880; 95% confidence interval (CI) 0.797–0.972; p = 0.011). In the pooled analysis no benefit on overall survival (OS: pooled HR = 0.957; 95%CI 0.900–1.017; p = 0.153), or progression-free survival (PFS: pooled HR = 0.908; 95%CI 0.817–1.010; p = 0.075) for targeted-based therapies as compared to conventional treatments could be demonstrated. No advantage was reported in response-rate (OR for RR = 1.210; 95%CI 0.990–1.478; p = 0.063). Begg's funnel plot showed no evidence of publication bias.
Conclusion: The use of molecular targeted agents does not translate into clinical benefit. Therefore, our work highlights the need to identify predictive factors for patient selection and rationally designed clinical trials.

Background

Advanced pancreatic cancer (APC) is the fourth leading cause of cancer-related death worldwide [1]. The incidence of this disease ranges from 1 to 10 cases per 100.000 people, being higher in developed countries and this finding has been related to cancer promoting western lifestyle [2]. It is more common in men than in women and the median age of diagnosis is 71 years. The overall 5-years survival rate is 3–5% with a median survival of 6 months [3]. Due to the challenging problems related to early diagnosis, almost 90% of cases are diagnosed at advanced stage. The clinical management of APC relies on a multidisciplinary approach based on systemic chemotherapy and may include radiation therapy and surgery, although the impact of therapy is merely palliative [4].

In the attempt to improve the outcome of APC patients, many drugs have been evaluated so far [5]. In the last 20 years, several trials have demonstrated that monotherapy regimens provided survival benefit [6,7]. Recent, studies investigating combination chemotherapy demonstrated an advantage in term of survival and clinical benefit as compared to single agents. The most effective approaches were FOLFIRINOX (5-fluorouracil, irinotecan and oxaliplatin) and gemcitabine-based doublets, with either platinum

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salts or fluoropyrimidines or nab-paclitaxel [8–11]. These findings have changed the current clinical practice. Moreover, the results of recent meta-analysis performed by our group, confirmed the role of combination chemotherapy in first line of treatment and underlined the marginal role of targeted therapy in combination with gemcitabine [12]. While the standard of care in first line treatment is well established, to date none of the evaluated therapeutic regimens demonstrated benefits in subsequent treatment lines [13]. However, even within the optimal setting, the patient outcome is poor and there is an urgent need of better understanding of APC pathogenesis in order to identify novel active approaches.

Peculiar genetic alterations have been identified that are considered play a major role in APC pathogenesis. These events impair different signaling pathways, such as EGFR-RAS-MEK-ERK, PI3K-AKT-mTOR, VEGF-VEGFR and Hedgehog, that may represent potential therapeutic targets [13–15]. Several randomized clinical trials (RCTs) investigated the role of targeted therapy in APC [16]. Unfortunately, all the studies failed to demonstrate a relevant improvement in clinical outcome despite statistical significant results. Among these, it is worth to mention that the trial comparing erlotinib (a selective EGFR tyrosine kinase inhibitor) *plus* gemcitabine *versus* gemcitabine alone demonstrated a minimal but statistically significant 2-weeks improvement in median overall survival (OS) for the experimental arm [17]. Moreover, targeting both VEGF and mTOR pathways, evaluated in small RCTs, did not show any benefit [18,19]. Finally, the combination of the Hedgehog inhibitor vismodegib *plus* gemcitabine did not improve tumor response-rate (RR) and OS [20]. Therefore the role of targeted-based treatment in APC is still uncertain. At this aim, we performed a systematic review to aggregate available data for each pathway evaluated in the management of APC.

Methods

Study design

In order to clarify the clinical impact of targeted therapy in the management of APC, we evaluated prospective and RCTs that compared a targeted therapy-based treatment with a conventional regimen and performed a systematic review and meta-analysis. OS, progression-free survival (PFS) and RR were considered predefined endpoints to verify the efficacy in term of clinical outcome.

Searching

As performed in our previous works, bibliographic research was conducted by PubMed, the Central Registry of Controlled Trials of the Cochrane Library and Embase, and ESMO/ASCO abstracts (the major international annual meetings). We identified a time frame comprises between January 2007, the release year of erlotinib in clinical practice, and March 2015 [17]. The risk of selection and/or information bias was minimized by including prospective studies only [21–23]. The following key-words were used to perform our search: “pancreatic”, “tumor”, “cancer”, “advanced”, “metastatic”, “therapy”, “targeted”, “prospective”, and “randomized” in different combinations: i.e. “advanced pancreatic cancer, targeted therapy”. We used references reported in each study evaluated and pubmed ‘related articles’ function in order to identify all studies potentially eligible. In our searching strategy we considered only English language.

Selection

The main characteristics of the trials included in the present review are reported in Table 1.

Inclusion criteria

We evaluated RCTs enrolling patients with APC diagnosis. We considered abstracts or unpublished reports that contain sufficient retrievable data on population characteristics, specific interventional approach with related outcomes. Experimental arm incorporated a targeted agent. A conventional schedule was administered in the control arm.

Exclusion criteria

Absence of data on at least one predefined end-point; no concomitant irradiation or non-systemic modalities of administration of therapeutic agents.

Data extraction

Two independent investigators (D.C. and N.S.) selected and examined eligible studies [24]. In according to the PRISMA criteria, they extracted and evaluated publication year, patients' number, treatment schedule and efficacy results as variables obtained by selected trials [25]. An arbiter (P.T.) interpreted and resolved potential discrepancies.

Validity assessment

The Cochrane reviewers' handbook for 5 requirements was used to determine the quality assessment of selected studies [26,27]. 24 trials A (low risk of bias), 1 trial B (intermediate risk of bias), and 2 trials C (high risk of bias) were described (Table 2).

Quantitative data synthesis

The effects of the targeted-based treatments [biological ± chemotherapeutic agents] were evaluated on the pre-specified end-points carrying out a meta-analysis [28]. About the efficacy end-points, survival data were extracted as Hazard Ratios (HRs) of OS, and PFS with relative confidence intervals (95%CI). The interaction between survival and experimental treatment was obtained by each study from the HRs logarithm. The overall effect of combined treatments on RR was calculated using methods for dichotomous data (odds ratio and risk ratio assessment; 95%CI). Heterogeneity between the trials was assessed by Cochrane's Q-test and I^2 statistics. We evaluated several trials that compared targeted agents with different mechanisms of action. For this reason the random-effects model was preferred for the analysis [29]. Pooled data analysis was performed according to the DerSimonian and Laird test [30,31]. We investigated the presence of publication biases using Begg's test and visual inspection of funnel plots [32]. A two-tailed p value equal or lower than 0.05 was considered statistically significant. The software STATA SE v. 13.1 (STATA_ Corporation, Texas, USA) was used to perform all the statistical analyses [33]. The statistical methods of this study were reviewed by the Laboratory of Bioinformatics and Biostatistics of Department of Medical and Surgical Sciences at University of Magna Graecia, Catanzaro, Italy.

Results

Studies selection and characteristics

RCTs selection and search strategy were showed in the PRISMA chart, as reported in Fig. 1. In the present systematic review we considered the time-frame between 2007 and 2015. The preliminary searching results reported 1119 + 93 studies, as meeting

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