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.

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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 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 statistically 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 end-points 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 I² 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 Beggs’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
selected and included in the initially excluded, while 460 were excluded for unmet selection criteria. Because of study design, 725 studies were RR; odds ratio, OR; TT: target therapy; X: conventional therapy; observation, OBS. GEM
Main characteristics of the randomized trials included in the meta-analysis. Abbreviations: overall survival, OS; progression free survival, PFS; hazard ratio, HR; response-rate, RRR; Cetuximab; CIX; Trametinib 160 18 22 0.98 0.93
Table 1
Final analysis. Among 4 trials that contain multiple arms comparison, each comparison was reported separately [34-37]. Finally, one trial evaluated targeted therapy only in maintenance setting [38]. All RCTs previously selected, provided a gemcitabine-based schedule both in experimental and non-experimental arms. GEM
absolutes and full papers. Because of study design, 725 studies were initially excluded, while 460 were excluded for unmet selection criteria. Twenty-seven trials for a total of 8205 patients were selected and included in the final analysis. Among 4 trials that

Table 1
Included studies Method of randomization Allocation concealment Blind Withdrawal and dropout Baseline Quality level
Moore [17] 2007 GEM vs GEM + ERLOTINIB 569 8 9 0.82 0.77
Kindler [18] 2010 GEM vs GEM CAP vs GEMCAP + CV1001 708 18 9 1.19 1.5
Middleton (2) [36] 2014 GEMCAP vs GEMCAP + CV1001 708 18 9 1.19 1.5
Middleton (1) [36] 2014 GEMCAP vs GEMCAP + CV1001 708 18 9 1.19 1.5
Scott [56] 2015 GEM vs GEM + RIGOSERTIB 160 13 19 1.24 0.96
Deplanque [57] 2013 GEM vs GEM + MASTITINIB 348 NR NR 0.9 0.87
Yamaue [53] 2015 GEM vs GEM + ELAPOMOTIDE 153 NR NR 0.9 0.87
Van Cutsem [55] 2015 GEM vs GEM + PIMASERTIB 88 9 9 NR NR 0.8 0.88
Dalgleish [58] 2015 GEM vs GEM + IMM101 110 NR NR 0.6 0.51
Moore [17] 2007 GEM vs GEM + ERLOTINIB 569 8 9 0.82 0.77
Kindler [18] 2010 GEM vs GEM + BEVA 602 10 13 0.96 NR
Philip [39] 2010 GEM vs GEM + CET 745 14 12 0.94 NR
Kindler [40] 2011 GEM vs GEM + AXI 632 2 5 1.01 NR
Spano [41] 2008 GEM vs GEM + AXI 103 3 7 0.71 NR
Richards [42] 2011 GEM vs GEM + ENZ 121 5 9 NR NR
Wolpin [44] 2011 GEM vs GEM + ACS 196 NR NR 0.78 0.84
Bergmann [54] 2015 GEM vs GEM + SUN 106 7 6 NR NR

Table 2
Quality assessment.
Included studies Method of randomization Allocation concealment Blind Withdrawal and dropout Baseline Quality level
Moore Centralized Central office Yes Detailed criteria Identical baseline A
Kindler Centralized Central office Yes Detailed criteria Identical baseline A
Philip Centralized Central office No Detailed criteria Identical baseline A
Kindler Centralized Central office Yes Detailed criteria Identical baseline A
Spano Centralized Central office No Detailed criteria Identical baseline A
Richards Centralized Central office No Detailed criteria Identical baseline A
Goncalves Centralized Central office Yes Detailed criteria Identical baseline A
Senderowicz Centralized Central office Yes Detailed criteria Identical baseline A
Eckhardt Centralized Central office Yes Detailed criteria Identical baseline A
Rougier Centralized Central office No Detailed criteria Identical baseline A
Philip Centralized Central office No Detailed criteria Identical baseline A
Sorafenib; ERL
Sorafenib; ENZ
Moore et al. / Pancreatology 16 (2016) 249–258
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control arms [17,18,34–58]. Among these, 3 studies were designed with combinatory gemcitabine-based schedule [36,48,49]. All selected RCTs that included at least one retrievable arms-comparison in terms of OS, PFS or RR were reported. In the final analyses, 27 trials were included. 23 out of 27 were eligible for OS analysis (8 with an anti-angiogenic agent; 4 with an anti-EGFR agent; 3 with an anti-IGFR1 agent and 2 with an immune-modulation strategy; 6 single trials investigating an anti-PI3K, a FTASE inhibitor, an anti-MEK, an anti-PSCA, a c-KIT inhibitor and an apoptosis inhibitor, respectively); 18 out of 27 were eligible for PFS analysis (4 studies containing an anti-angiogenic drug; 4 containing an anti-EGFR drug; 3 studies containing an anti-IGFR1 drug; 2 containing an immune-modulation strategy; 2 with anti-MEK drug; 3 single trials investigating an anti-PI3K, an anti-PSCA, and an apoptosis inhibitor, respectively). 23 out of 27 were evaluable for RR analysis (8 with an anti-angiogenic agent; 4 with an anti-EGFR agent; 3 with an anti-IGFR1 agent; 2 with an anti-MEK agent; 6 single trials investigating an immune-modulator, an anti-PI3K, an anti-urokinase, an apoptosis inhibitor, an anti-HMG-CoA and an anti-PSCA, respectively).

OS analyses

Five trials were excluded from OS analysis because of missing data. In our analysis targeted therapy plus conventional therapy did not demonstrate any survival advantage in APC patients as compared to conventional therapy alone (pooled HR 0.957; 95%CI 0.900–1.017; p = 0.153; Fig. 2). We reported the subgroup analysis stratified for the targeted pathways. In particular, we showed a significant OS benefit for anti-EGFR agents only (HR 0.880; 95%CI 0.797–0.972; p = 0.011). No statistically significant difference was found for other pathways. We performed a subgroup meta-analysis considering two study populations, the trials evaluated in the previous meta-analysis (first) and the trials retrieved by new database search (second), without evidence of significant differences in the two groups (Supplementary data, Fig. S).

PFS analyses

PFS data were not provided in 10 trials that were therefore excluded from PFS analysis. Targeted therapy-based treatments failed to demonstrate a significant benefit in terms of PFS as compared to a conventional treatment (pooled HR 0.908; 95%CI 0.817–1.010; p = 0.075; Fig. 3). No advantage was demonstrated by the analysis for single pathway.

RR analyses

Five trials did not report data in terms of RR, and were excluded from this analysis. No advantage was observed in term of RR (OR for RR 1.210; 95%CI 0.990–1.478; p = 0.063; Fig. 4). In the single pathway analysis we found a significant improvement (OR for RR 2.621; 95%CI 1.117–6.149; p = 0.027) for anti-urokinase drugs.
Risk of bias in individual studies

Using Begg's funnel plot we did not detect a significant presence of publication bias. Funnel plots showed substantial symmetry (Fig. 5).

Discussion

Our meta-analysis of 27 RCTs for a total of 8205 patients explored the available evidence about the efficacy of targeted therapy in APC by comparing an experimental regimen including a targeted agent to any other treatment. A meta-analysis stratified for each involved pathway was performed. Our study did not show any survival benefit (OS: pooled HR 0.957; PFS: pooled HR 0.908) for targeted therapy on its whole. Indeed, for the majority of selected pathway inhibitors, no survival benefit was observed. Only sub-group analysis investigating anti-EGFR agents demonstrated a significant, but marginal, advantage in OS (HR 0.880). In terms of RR results, we reported a significant improvement for urokinase targeting agent only. These findings suggest that the inclusion of the targeted therapy should not be an option in the neoadjuvant, second-line and maintenance settings, while it is an effective
approach in other cancers. Taking into account these findings, we may afford some possible explanations which are summarized here.

Our results reflect the common clinical practice that is focused on conventional agents. Indeed, only few trials, designed on targeted-based treatment, reached their primary endpoint in term of survival outcome. It is likely that this finding is potentially related to the low number of enrolled patients in the single trials and to the statistical design that, probably, overestimated the expected benefit and led to non-powered studies. We pointed out that the absence of a patient stratification and a priori selection represents the major limit of trials included in our meta-analysis. A possible explanation of this limitation for all targeted pathways, is the lack of recognized previously validated predictive biomarkers. Moreover, it is interesting to consider that, despite patients were not selected, anti-EGFR agents met the meta-analytic endpoint of increased survival, allowing us to hypothesize that these results could be underestimated in individual studies, as reported for other diseases in which activating EGFR mutations were identified as tumor molecular drivers with prognostic and predictive role [59,60]. Therefore, these results can be explained, as discussed in other works, with the high percentage of tumors harboring KRAS mutation, that likely inhibits upstream signaling proteins like EGFR [61,62].

A second point concerns the impact of immunobiology of pancreatic tumors, a recently demonstrated hallmark of cancer [63]. APC, however, has been historically considered a non-immunogenic tumor, mainly because of the low amount of cytotoxic tumor infiltrating lymphocytes (TILs) [64,65]. Indeed, there is not meta-analytic evidence that immunotherapy-based treatments, which have been selected in the present work, are able to produce any benefit. However, these studies only included a

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### Table: Treatment Comparison

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Treatment</th>
<th>HR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mooney[23]</td>
<td>2007</td>
<td>GEM vs GEM+ERLOTINIB</td>
<td>0.77 (0.64, 0.92)</td>
<td>6.68</td>
</tr>
<tr>
<td>Philip[19]</td>
<td>2010</td>
<td>GEM vs GEM+CET</td>
<td>1.07 (0.93, 1.24)</td>
<td>7.43</td>
</tr>
<tr>
<td>Senderowicz[24]</td>
<td>2007</td>
<td>GEM vs GEM+ERLOTINIB</td>
<td>0.76 (0.54, 0.92)</td>
<td>5.58</td>
</tr>
<tr>
<td>Propper[25]</td>
<td>2014</td>
<td>GEM vs GEM+ERLOTINIB</td>
<td>0.63 (0.63, 1.10)</td>
<td>5.40</td>
</tr>
<tr>
<td>Subtotal (I-squared = 79.8%, p = 0.016)</td>
<td></td>
<td>0.68 (0.71, 1.04)</td>
<td>25.30</td>
<td></td>
</tr>
<tr>
<td>Goncalves[26]</td>
<td>2012</td>
<td>GEM vs GEM+SORA</td>
<td>1.04 (0.70, 1.54)</td>
<td>3.93</td>
</tr>
<tr>
<td>Roulier[27]</td>
<td>2012</td>
<td>GEM vs GEM+AFL</td>
<td>1.02 (0.63, 1.25)</td>
<td>6.52</td>
</tr>
<tr>
<td>Casper[28]</td>
<td>2014</td>
<td>GEM+CIS vs GEM+CIS+SOR</td>
<td>0.92 (0.62, 1.35)</td>
<td>3.99</td>
</tr>
<tr>
<td>Renf[29]</td>
<td>2013</td>
<td>OBS vs SUNITINIB</td>
<td>0.51 (0.29, 0.89)</td>
<td>2.53</td>
</tr>
<tr>
<td>Subtotal (I-squared = 44.6%, p = 0.144)</td>
<td></td>
<td>0.91 (0.71, 1.16)</td>
<td>16.98</td>
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<tr>
<td>Wolp[30]</td>
<td>2013</td>
<td>GEM vs GEM+AGS</td>
<td>0.84 (0.61, 1.15)</td>
<td>4.67</td>
</tr>
<tr>
<td>Subtotal (I-squared = .%, p = .)</td>
<td></td>
<td>0.84 (0.61, 1.15)</td>
<td>4.67</td>
<td></td>
</tr>
<tr>
<td>Philip[31]</td>
<td>2014</td>
<td>GEM+ERL vs GEM+ERL+CIX</td>
<td>1.00 (0.68, 1.44)</td>
<td>4.15</td>
</tr>
<tr>
<td>Kindler (1)[32]</td>
<td>2012</td>
<td>GEM vs GEM+GANTITUMAB</td>
<td>0.65 (0.41, 1.04)</td>
<td>3.24</td>
</tr>
<tr>
<td>Fuchs (1)[33]</td>
<td>2015</td>
<td>GEM vs GEM+GANTITUMAB</td>
<td>1.00 (0.64, 1.20)</td>
<td>6.30</td>
</tr>
<tr>
<td>Fuchs (2)[33]</td>
<td>2015</td>
<td>GEM vs GEM+GANTITUMAB</td>
<td>0.97 (0.67, 1.12)</td>
<td>2.61</td>
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<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.399)</td>
<td></td>
<td>0.96 (0.65, 1.09)</td>
<td>20.44</td>
<td></td>
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<td>Kindler (2)[32]</td>
<td>2012</td>
<td>GEM vs GEM+CONATUMUMAB</td>
<td>0.65 (0.41, 1.05)</td>
<td>3.20</td>
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<tr>
<td>Subtotal (I-squared = .%, p = .)</td>
<td></td>
<td>0.65 (0.41, 1.04)</td>
<td>3.20</td>
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<tr>
<td>Infante[34]</td>
<td>2014</td>
<td>GEM vs GEM+TRAMETINIB</td>
<td>0.93 (0.65, 1.34)</td>
<td>4.30</td>
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<tr>
<td>Van Cutsem[35]</td>
<td>2015</td>
<td>GEM vs GEM+PIMASERTIB</td>
<td>0.88 (0.55, 1.42)</td>
<td>3.17</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.856)</td>
<td></td>
<td>0.91 (0.66, 1.21)</td>
<td>7.47</td>
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<tr>
<td>Middleton[36]</td>
<td>2014</td>
<td>GEMCAP vs GEMCAP+GV1001</td>
<td>1.50 (1.02, 2.08)</td>
<td>7.01</td>
</tr>
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<td>Middleton[36]</td>
<td>2014</td>
<td>GEMCAP vs GEMCAP+GV1001</td>
<td>1.00 (0.84, 1.19)</td>
<td>6.99</td>
</tr>
<tr>
<td>Dalgleish[37]</td>
<td>2015</td>
<td>GEM vs GEM+IMM-101</td>
<td>0.65 (0.32, 0.81)</td>
<td>3.25</td>
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<tr>
<td>Subtotal (I-squared = 91.4%, p = 0.000)</td>
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<td>0.96 (0.61, 1.52)</td>
<td>17.25</td>
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<td>Scott[38]</td>
<td>2015</td>
<td>GEM vs GEM+RIGOSERTIB</td>
<td>0.96 (0.68, 1.36)</td>
<td>4.49</td>
</tr>
<tr>
<td>Subtotal (I-squared = .%, p = .)</td>
<td></td>
<td>0.96 (0.68, 1.36)</td>
<td>4.49</td>
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</tr>
</tbody>
</table>

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**Fig. 3.** Comparison of PFS according to involved pathway. Abbreviation: progression free survival, PFS.
cancer vaccine and an immune-adjuvant. Due to the increasing knowledge on the role played by tumor associated macrophages, myeloid derived suppressor cells and cancer associated fibroblasts in cancer evasion from immunosurveillance, new immunotherapeutic approaches are eagerly awaited [64–66]. Furthermore, clinical trials including checkpoint-inhibitors such as ipilimumab, nivolumab and pembrolizumab are currently ongoing even if with mixed results [65,67].

Finally, our meta-analysis presents the following limitations: it is not based on individual patient data which makes not feasible to retrieve data about the corresponding end-points from all the studies; in our analysis the targeted agents are a potential generator of biases taking into account a substantial heterogeneity in the included trials. Moreover, the analysis includes multiple trials for just one drug. For instance erlotinib has been evaluated in several trials which diverging results. The low entity of the reported advantages has precluded usage of erlotinib in the common practice regardless FDA and EMA approvals.

Our meta-analysis suggests the need of new trial design and underscore the need of novel preclinical findings with effective translation in clinical practice. At this aim, our data strongly support additional investigation concerning molecular pathogenesis

<table>
<thead>
<tr>
<th>Trials</th>
<th>Authors</th>
<th>YEAR</th>
<th>TREATMENT</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
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<tr>
<td>anti EGFR</td>
<td>Moreno[1] 2007</td>
<td>GEM vs GEM+ERLOTINIB</td>
<td>1.14 (0.42, 3.08)</td>
<td>3.76</td>
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<tr>
<td></td>
<td>Philip[2] 2010</td>
<td>GEM vs GEM+CET</td>
<td>0.84 (0.37, 1.91)</td>
<td>5.86</td>
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<td>Senderowicz[3] 2007</td>
<td>GEM vs GEM+ERLOTINIB</td>
<td>1.14 (0.42, 3.08)</td>
<td>3.76</td>
<td></td>
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<tr>
<td></td>
<td>Propper[4] 2014</td>
<td>GEM vs GEM+ERLOTINIB</td>
<td>0.24 (0.03, 2.21)</td>
<td>0.81</td>
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<td></td>
<td>Subtotal (I-squared = 0.0%, p = 0.614)</td>
<td></td>
<td>0.92 (0.55, 1.56)</td>
<td>13.80</td>
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<td>anti angiogenesis</td>
<td>Kindler[5] 2010</td>
<td>GEM vs GEM+BEV</td>
<td>1.34 (0.56, 3.23)</td>
<td>4.76</td>
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<td></td>
<td>Kindler[6] 2011</td>
<td>GEM vs GEM+AXI</td>
<td>2.69 (0.49, 13.62)</td>
<td>1.41</td>
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<tr>
<td></td>
<td>Span[7] 2008</td>
<td>GEM vs GEM+AXI</td>
<td>2.42 (0.61, 8.69)</td>
<td>2.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Richard[8] 2011</td>
<td>GEM vs GEM+ENZ</td>
<td>1.86 (0.61, 5.28)</td>
<td>2.96</td>
<td></td>
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<tr>
<td></td>
<td>Gencaru[9] 2012</td>
<td>GEM vs GEM+BORA</td>
<td>1.27 (0.64, 2.52)</td>
<td>7.37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cagasi[10] 2014</td>
<td>GEM+CIS vs GEM+CIS+SQR</td>
<td>0.74 (0.16, 3.41)</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bergman[11] 2015</td>
<td>GEM vs GEM+SUNITINIB</td>
<td>1.16 (0.38, 3.64)</td>
<td>2.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reshi[12] 2013</td>
<td>OBS vs SUNITINIB</td>
<td>[Excluded]</td>
<td>0.00</td>
<td></td>
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<tr>
<td></td>
<td>Subtotal (I-squared = 0.0%, p = 0.999)</td>
<td></td>
<td>1.42 (0.95, 2.11)</td>
<td>23.18</td>
<td></td>
</tr>
<tr>
<td>anti PSMA</td>
<td>Wogelo[13] 2013</td>
<td>GEM vs GEM+AGS</td>
<td>1.89 (0.89, 4.00)</td>
<td>6.26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (I-squared = , %, p = )</td>
<td></td>
<td>1.89 (0.89, 4.00)</td>
<td>6.26</td>
<td></td>
</tr>
<tr>
<td>anti PI3K</td>
<td>Kindler (2)[14] 2012</td>
<td>GEM vs GEM+CONATUMAB</td>
<td>1.00 (0.20, 5.08)</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (I-squared = , %, p = )</td>
<td></td>
<td>1.00 (0.20, 5.08)</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td>anti MEK</td>
<td>Infante[15] 2014</td>
<td>GEM vs GEM+TRAMETINIB</td>
<td>1.28 (0.64, 2.58)</td>
<td>7.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Van Cutsem[16] 2015</td>
<td>GEM vs GEM+PIMAERTIBI</td>
<td>1.00 (0.36, 2.63)</td>
<td>3.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (I-squared = 0.0%, p = 0.993)</td>
<td></td>
<td>1.16 (0.57, 2.39)</td>
<td>11.99</td>
<td></td>
</tr>
<tr>
<td>anti HMGI-CoA</td>
<td>Hong[17] 2014</td>
<td>GEM vs GEM+SIMVASTATIN</td>
<td>0.48 (0.18, 1.20)</td>
<td>4.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (I-squared = , %, p = )</td>
<td></td>
<td>0.46 (0.18, 1.20)</td>
<td>4.07</td>
<td></td>
</tr>
<tr>
<td>anti urokinase</td>
<td>Heinemann(1)[18]2013</td>
<td>GEM vs GEM+UPAMOSTAT</td>
<td>1.81 (0.51, 6.38)</td>
<td>2.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heinemann(2)[19]2013</td>
<td>GEM vs GEM+UPAMOSTAT</td>
<td>3.59 (1.13, 11.41)</td>
<td>2.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (I-squared = 0.0%, p = 0.432)</td>
<td></td>
<td>2.62 (1.12, 6.15)</td>
<td>5.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall (I-squared = 8.0%, p = 0.349)</td>
<td>1.21 (0.99, 1.48)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Fig. 4. Comparison of RR according to involved pathway. Abbreviation: response-rate, RR; odds ratio, OR; TT: target therapy; X: conventional therapy.
of APC, in order to discover both new potential targets and predictive biomarkers.

Moreover, if we compare our previous meta-analysis to this update as far as it concerns analysis of targeted therapy only, it is easy to observe similar findings. It is likely that our negative results are due to the lack of a significant “evolution” in trial design, unchanged if compared to ten years ago. On these bases, future trial design should benefit from the introduction of new technologies such as next generation sequencing (NGS) to define enrollment of patients based on specific molecular alterations [68]. Along the same line, a recently published study on gene expression analysis has identified human tumor subtypes (classical, quasimesenchymal and exocrine-like) that presented a distinguished clinical outcome and a different sensitivity to treatment [69].

Another critical point is represented by the chemotherapy scaffold: both the use of gemcitabine alone or in old combination schedules and the absence of targeted therapy combination with the current golden standard (e.g. gemcitabine plus nab-paclitaxel or FOLFIRINOX). Recent trials have been designed taking into account these strategies chosen on the basis of patient performance status [70,71].

In conclusion, our work confirms the previously reported meta-analytic findings and provides the first proof-of-concept that targeted therapy is an ineffective therapeutic approach against APC, unable to modify disease outcome [61,72].

In a prognostically poor disease as APC, an improvement of clinical outcome is still possible with the identification of the “right drug for the right patient” only. Well-designed biomarker-driven clinical trials are eagerly awaited to optimize the management of APC patients.

Author contributions

CD, SN, TP, and TP designed the study. CD, SN, CS did the literature search, and extracted data. CD realized the figures. CS performed the tables. All authors collected data. CD, SN, BC, TP, and TP interpreted and analyzed the data, and wrote the manuscript. All authors read, and approved final version of the manuscript.

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Appendix A. Supplementary data

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References


