Original Research

A randomised phase 2 trial of nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in locally advanced or borderline resectable pancreatic adenocarcinoma

Michele Reni a,*, Silvia Zanon a, Gianpaolo Balzano b, Paolo Passoni c, Chiara Pircher a, Marta Chiaravalli a, Clara Fugazza a, Domenica Ceraulo a, Roberto Nicoletti d, Paolo Giorgio Arcidiacono e, Marina Macchini a, Umberto Peretti a, Renato Castoldi b, Claudio Doglioni f,g, Massimo Falconi b,g, Stefano Partelli b, Luca Gianni a

a Department of Medical Oncology, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy
b Pancreatic Surgery Unit, Pancreas Translational & Clinical Research Center, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy
c Department of Radiotherapy, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy
d Department of Radiology, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy
e Pancreato-Biliary Endoscopy and Endosonography Division, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy
f Pathology Unit, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy
g Università Vita e Salute, Milan, Italy

Received 10 April 2018; received in revised form 29 June 2018; accepted 8 July 2018

**KEYWORDS**
Pancreatic cancer; Borderline resectable disease; Locally advanced disease; Chemotherapy;

**Abstract**

**Background:** The current trial assessed whether the addition of cisplatin and capecitabine to the nab-paclitaxel–gemcitabine backbone is feasible and active against borderline and locally advanced pancreatic adenocarcinoma (PDAC).

**Method:** Fifty-four chemo-naive patients, aged between 18 and 75 years, with a pathological diagnosis of locally advanced or borderline resectable PDAC were randomised to receive either nab-paclitaxel, gemcitabine, cisplatin and oral capecitabine (PAXG; arm A; N = 26) or nab-paclitaxel followed by gemcitabine (AG; arm B; N = 28).

---

* Corresponding author.
E-mail address: reni.michele@hsr.it (M. Reni).

https://doi.org/10.1016/j.ejca.2018.07.007
0959-8049/© 2018 Elsevier Ltd. All rights reserved.
Pancreatic adenocarcinoma (PDAC) is the fifth cause of death in cancer patients [1]. About 80% of cases present at diagnosis a locally advanced or metastatic disease. In metastatic disease, combination chemotherapy is the standard treatment due to the improved overall survival (OS) over gemcitabine [2–4]. Despite the absence of randomised data, the same chemotherapy used for metastatic disease is commonly recommended also in borderline/locally advanced disease. Several reasons concur with the lack of adequate level of evidence. The most relevant reason is that most randomised clinical trials did not complete the planned accrual [5–7]. In addition, the definition of locally advanced and borderline resectability is heterogeneous, changed over time and is different across institutions. The aforementioned facts hamper the comparability of different reports, wider applicability [8] and interpretation of the results. Finally, radiological assessment to define resectability relies on centre volume [9] and on intrinsic limits of the instrument [10].

We have recently reported the results of a phase Ib trial conducted to determine the recommended phase II dose of nab-paclitaxel in combination with cisplatin, capecitabine and gemcitabine (PAXG regimen) [11]. The scientific rationale has been previously reported [11] and comprises the well-known synergism of taxanes with fluoropyrimidines, cisplatin and gemcitabine [4,12,13]. The regimen showed an encouraging preliminary antitumour activity for patients with chemo-naive, borderline or locally advanced pancreatic cancer. Herein, we report the results of an open-label, single institution, randomised phase II trial that explored the feasibility and antitumour activity of either nab-paclitaxel plus gemcitabine (AG) or the PAXG regimen in patients with locally advanced or borderline resectable PDAC (NCT01730222). The primary end-point was the tumour resection rate. If at least four such resections were performed, the treatment was considered as active. The secondary end-points were progression-free survival (PFS), overall survival (OS), Response Evaluation Criteria in Solid Tumours response rate, Hartmann’s pathologic response, carbohydrate antigen 19.9 response rate and toxicity.

**Results:** Eight patients (31%) in the PAXG arm and nine (32%) in the AG arm underwent resection. PFS at 1-year was 58% in arm A and 39% in arm B. OS at 18-month was 69% in arm A and 54% in arm B.

**Conclusions:** In this phase II study, the addition of cisplatin and capecitabine to the AG backbone was feasible and yielded promising results in terms of disease control without detrimental impact on tolerability. The approach warrants further investigation in a phase III study.

**Trial registration:** NCT01730222.

© 2018 Elsevier Ltd. All rights reserved.
generated code to receive either an intravenous infusion of nab-paclitaxel at 150 mg/m², followed by gemcitabine at 800 mg/m², cisplatin at 30 mg/m² on day 1 and 15 and oral capecitabine at 1250 mg/m² on days 1–28 (arm A) or an intravenous infusion of nab-paclitaxel at 125 mg/m² followed by gemcitabine at 1000 mg/m² on days 1, 8 and 15 (arm B). Nab-paclitaxel was provided for free by Celgene S.r.l., Italy, for both arms. Patients were enrolled by the attending oncologist who registered them at an internal clinical research assistant team that conserved the randomisation list and was also responsible for data collection in an electronic database, monitoring accuracy, completeness and reliability of the acquired data.

Patients were stratified by a baseline carbohydrate antigen 19.9 (CA19.9) level (<10 × ULN versus ≥10 × ULN). The surgical classification (i.e. borderline versus locally advanced) was not used as a stratification factor because prognostic validation was missing [17]. In both arms, treatment was administered every 28 d (1 cycle) and continued until progressive disease, unacceptable level of adverse events, patient’s refusal or medical decision. In all other cases, considering the absence of data on optimal treatment duration, chemotherapy was administered for a minimum of 6 cycles. Afterwards treatment was continued in case of clinical benefit. At any radiological assessment, patients were evaluated for surgery. Evaluation of resectability was performed during a multidisciplinary meeting with the participation of both expert radiologists and high-volume surgeons. Surgery was indicated when a gross radical resection could be predicted, in absence of radiological or biological (CA19.9) tumour progression.

At the end of 6 cycles of chemotherapy, patients who were unsuitable for resection and were still progression free received concomitant chemoradiotherapy consisting of oral capecitabine at 1250 mg/m²/daily and of 40–44.25 Gy by tomotherapy in 15 fractions. The same chemoradiation was also recommended after resection.

A basal CT or magnetic resonance scan of the chest, abdomen and pelvis was performed within 3 weeks before randomisation. A radiologist, blinded to the treatment arm, assessed tumour response using the revised RECIST, 1.1, guidelines [16] every 8 weeks until disease progression or in the case of any symptom suggestive of disease progression. Tumour markers were assessed every 4 weeks. The worst toxicity observed for each patient was recorded.

The primary end-point of the study was the percentage of patients undergoing a microscopically radical (R0) or non-radical (R1) surgery after chemotherapy. The secondary end-points were progression-free survival (PFS), defined as the time from the day of randomisation to the disease progression or death for any cause, whichever occurred first; OS, defined as the time interval between randomisation and the date of death or of the last follow-up visit and radiological, pathological [18] and biochemical response rate [19]. Both the radiologist (R.N.) and the pathologist (C.D.) were blinded to the treatment arm. Toxicity was defined according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.

The database lock for the present analysis was 21 March 2018, when all living patients had completed at least 25 months of follow-up.

2.1. Statistical analysis

All primary analyses were based on the intention to treat, where all randomised patients had to be included. Safety analysis was performed on the safety population defined as all patients receiving at least one dose of study treatment. The study was designed as a calibrated phase II clinical trial. The A’Hern—single-stage phase II design was used [20]. The calibration group is not a control group in the traditional sense but is only used to evaluate whether the sample of patients who receive the investigational treatment has the capability of showing a response. This design has not the power for a head-to-head comparison. Accordingly, no formal efficacy comparison between the two groups was planned, and the analysis of therapeutic effect was performed separately for each arm. The null hypothesis that the proportion of patients resected after chemotherapy would be of 5% was verified against the alternative hypothesis with a two-tailed test. The total number of patients to consider in each group was 27. In case that at least four resections were performed, the null hypothesis had to be refused and the treatment had to be considered active. This design has an error = 5% and a power = 80% under the alternative hypothesis = 20%. PFS and OS were described using the Kaplan–Meier curves. All analyses were carried out using Statistica, 12.0, statistical package for Windows (StatSoft Inc, 2011, Tulsa, OK 74104, USA).

3. Results

Between April 2014 and February 2016, 54 patients were randomised at a single institution to receive PAXG (arm A; N = 26) or AG (arm B; N = 28; Table 1). All patients received the assigned treatment (Fig. 1). After chemotherapy, all patients with either locally advanced or T4 disease remained unresectable, eight patients (31%; 80% of borderline resectable; 62% of T3) in arm A and nine (32%; 60% of borderline resectable; 45% of T3) in arm B underwent surgery, after a partial response (five arm A; six arm B patients), a reduction of CA19.9 > 90% (one arm A patient), or an improvement of vascular contact despite stable radiological disease according to RECIST criteria (two arm A; three arm B patients). No difference was observed between the arms.
Table 1
Baseline characteristic of the patients according to the randomisation arm.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PAXG</th>
<th>AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Male/female</td>
<td>13/13</td>
<td>7/21</td>
</tr>
<tr>
<td>KPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90–100</td>
<td>24 (86%)</td>
</tr>
<tr>
<td></td>
<td>70–80</td>
<td>7 (27%)</td>
</tr>
<tr>
<td>Age</td>
<td>61</td>
<td>66</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessel invasion a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior mesenteric/portal vein</td>
<td>14 (88%)</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>Hepatic artery</td>
<td>6 (38%)</td>
<td>6 (43%)</td>
</tr>
<tr>
<td>Superior mesenteric artery</td>
<td>12 (75%)</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>Celiac axis</td>
<td>8 (50%)</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>Borderline</td>
<td>10 (38%)</td>
<td>15 (54%)</td>
</tr>
<tr>
<td>Vessel invasion a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior mesenteric/portal vein</td>
<td>9 (90%)</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>Hepatic artery</td>
<td>1 (10%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Superior mesenteric artery</td>
<td>2 (20%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Celiac axis</td>
<td>1 (10%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>T3</td>
<td>11 (42%)</td>
<td>15 (54%)</td>
</tr>
<tr>
<td>T4</td>
<td>15 (58%)</td>
<td>13 (46%)</td>
</tr>
<tr>
<td>Head</td>
<td>18 (69%)</td>
<td>20 (71%)</td>
</tr>
<tr>
<td>Biliary stent</td>
<td>14 (54%)</td>
<td>15 (54%)</td>
</tr>
<tr>
<td>CA19.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>22 (85%)</td>
<td>21 (75%)</td>
</tr>
<tr>
<td>Median U/ml</td>
<td>287</td>
<td>278</td>
</tr>
<tr>
<td>Range</td>
<td>92–987</td>
<td>58–12,473</td>
</tr>
</tbody>
</table>

PAXG, cisplatin, nab-paclitaxel, capecitabine, gemcitabine; AG, nab-paclitaxel, capecitabine; KPS, Karnofsky Performance Status; CA19.9, carbohydrate antigen 19.9; ULN, upper limit of laboratory normal values.

* Percentages add to more than 100% because some patients having more than one vessel invaded.

in terms of surgical outcomes (Table 2). Pathological results are reported in Table 3.

Progression occurred in 22 (85%) arm A patients and in 27 (96%) arm B patients. Median PFS was 12.5 months (95% confidence interval [CI]: 10.8–14.6) in the PAXG arm and 9.9 months (95% CI: 7.2; 13.3) in the AG arm (Fig. 2). The rate of PFS at 6 and 12 months was 96% (95% CI: 90–100) and 58% (95% CI: 43–73) in the PAXG group, and 68% (95% CI: 54–82) and 39% (95% CI: 24–54) in the AG group, respectively.

The survival analysis was based on 19 deaths in arm A (73%) and 21 in arm B (75%). After a median follow-up of 30.9 months (range 25.1–43.9), the median survival was 20.7 months (95% CI: 14.5; 28.6) and 19.1 (95% CI, 11.5; 26.8) months and the 18-month survival rate was 69% (95% CI: 55–83) and 54% (95% CI: 39–69) in arm A and B, respectively (Fig. 3).

The response rate was 50% (95% CI: 35–65%) with PAXG and 36% (95% CI: 21–51%) with AG. A total of 22 (85%) patients in the PAXG arm and 21 (75%) patients in the AG arm had a baseline CA19.9 value higher than the upper limit of laboratory normal. A decrease of >50% was observed in 91% and 90% and a decrease of >90% in 41% (95% CI: 26–56) and 19% (95% CI: 7–31) of patients in arm A and B, respectively.

The median number of chemotherapy cycles was 5 (range: 3–7) in the PAXG group and 5 (range: 2–6) in the AG group, with 35% and 29% of patients, respectively, receiving treatment for at least 6 months. The number of administered cycles and reasons for interruption are reported in Table 4. In arm A, the median relative dose intensity was 82% for cisplatin, 79% for nab-paclitaxel, 77% for capecitabine and 72% for gemcitabine. In arm B, the median relative dose intensity was 78% for nab-paclitaxel and 77% for gemcitabine.

No fatal event was reported in both groups. Treatment-related adverse events of grade III or IV are reported in Table 5. Sepsis was reported in 4% of patients in arm B.

Chemoradiation was administered to 23 (88%) patients in PAXG arm and 16 (57%) patients in AG arm. Three patients in arm A did not receive chemoradiation due to progression of disease (N = 1), gastrointestinal bleeding (N = 1) and persistent haematologic toxicity (N = 1). Twelve patients in arm B did not receive chemoradiation due to progression of disease (N = 6), delayed post-surgical recovery (N = 1), refusal (N = 2), extrahaematologic toxicity (N = 2) and femoral fracture (N = 1). Subsequent therapy at time of progression was administered to 19/22 (86%) patients in arm A and 20/27 (74%) in arm B.

4. Discussion

This phase II trial was designed to evaluate the resectability rate of PAXG and AG regimens for patients with unresectable or borderline resectable PDAC. Both groups reached the primary end-point. This trial was run in a single institution removing bias with regard to surgical assessment, heterogeneity of the laboratory, radiologic staging and therapeutic management.

The resectability rate (31–32%) in the current trial is in the same order of magnitude of that reported with other treatment strategies. Namely, patients initially staged as having borderline/locally advanced disease could undergo resection after primary therapy with gemcitabine- or fluoropyrimidine-containing regimens, including or not including chemoradiation, in up to 23%–33% of cases [21–23]. Similarly, with more recent chemotherapy combinations such as folic acid, fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) or AG, the resection rate was in the range of 20–28% [22–25]. Despite similar resectability rates, median survival with ‘old’ regimens was apparently shorter (11.2–14.0 months) [21–23] compared with FOLFIRINOX or AG (8.9–25 months) [23–25, current series] and with PAXG (20.7 months in the present series). Resectability may be an inadequate and questionable...
surrogate end-point of chemotherapy efficacy because ‘local success’ does not necessarily correlate with the final outcome in a potentially micrometastatic disease. However, in borderline resectable/locally advanced PDAC, there is no validated alternative end-point for phase II trials. Resectability, R0 rate, PFS at variable timing, RECIST response, biochemical response, downstaging and pathological response have all been used as end-points. All such parameters have limitations, but the randomised design of the present study may reduce the biases in the interpretation of secondary end-points.

Both PAXG and AG were effective in terms of disease control. Moreover, observed toxicities were manageable and acceptable. Noteworthily, a partial response rate of 36% with AG arm in our trial is consistent with the 29% of rate previously reported in phase III trial for metastatic disease, as per investigator assessment [4]. Similarly, grade III–IV toxicities,
percentage of patients receiving 6 cycles (29\% in present trial versus 32\% in the MPACT trial) and the dose intensity (77\% for both drugs versus 81\% for nab-paclitaxel and 75\% for gemcitabine) were also consistent with the previous report [4]. Similarly, outcomes and toxicity data observed in the PAXG arm replicated prior phase I data [11].

Albeit the study design does not have power to perform head-to-head comparison and no difference between arms was evident in resection rates, PAXG regimen may provide potential advantages with respect to AG as regards to secondary end-points such as efficacy, activity, tolerability and logistical aspects. PAXG yielded a numerically larger number of RECIST and CA19.9 responses, a 28\% and 19\% more patients progression free at 6 months and 12 months, respectively. Numerically more pN0, pT0,2, marked/complete pathologic response and smaller residual tumours were
In summary, this phase II randomised trial investigated resection rate with two chemotherapy regimens without founding any difference between them. All other outcomes were secondary end-points, and this trial was not designed nor adequately powered to detect differences. Notwithstanding these considerations, the overall results of our study suggest that the addition of cisplatin and capecitabine to the AG backbone is feasible and is linked to very good control of the disease without a detrimental impact on tolerability. Accordingly, this regimen may be considered sufficiently promising to advice further testing in a phase III study.

Conflict of interest statement

Dr. Reni received grants, personal fees and non-financial support from Celgene, grants and personal fees from Baxalta and Merck-Serono, grants from Helsinn, personal fees from, Lilly, Pfizer, AstraZeneca, Novocure, Halozyne, Novartis, Shire. Dr. Gianni received personal fees from Roche, Pfizer, Boehringer Ingelheim, Celgene, Tahio Pharmaceutical, Synthon, AstraZeneca, Genomic Health, Merk Sharp & Dohme, Synaffix, Eli Lilly, Odonate Therapeutics, Sandoz, Onkaido, Oncolytics Biotech, ADC Therapeutics and Seattle Genetics. All remaining authors have declared no conflicts of interest.

Funding

Celgene provided funding for the study with an unrestricted grant and the supply of the drug. Celgene did not have any role in the study design; in the collection, analysis and interpretation of data; in the writing of the report and in the decision to submit the article for publication.

Availability of data and material

Original data can be found in patients’ medical record that is preserved in Medical Oncology Department archive. Paper case report forms and the electronic database generated from these are preserved in the archive of the clinical research assistant team.

Acknowledgements

Celgene (IIT28590) provided funding for the study with an unrestricted grant and the supply of the nab-paclitaxel. The authors are indebted to their patients and their families for their generous commitment.

References


