A dose escalation study of gemcitabine plus oxaliplatin in combination with imatinib for gemcitabine-refractory advanced pancreatic adenocarcinoma


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Background: Targeting platelet-derived growth factor receptor-β (PDGFR-β) is a potential strategy to reduce tumour-related interstitial fluid pressure, enhance cytotoxic drug uptake and reduce chemoresistance. This study aimed to define safe doses of gemcitabine plus oxaliplatin when combined with imatinib (potent PDGFR-β inhibitor) in patients with advanced gemcitabine-refractory pancreatic cancer (PC).

Patients and methods: Using a 3 + 3 dose escalation design, patients of performance status zero or one were entered into five sequential dose levels (DLs) of gemcitabine [day 1, from 400 (DL1) to 1000 mg/m² (DL4)] and oxaliplatin [day 2, 85 (DL1–4) and 100 mg/m² (DL5)] two weekly. Imatinib 400 mg od was given for 7 days (day minus 2–5) each cycle.

Results: Twenty-seven patients received 168 cycles in total. Median age was 61 years (44–74 years). Dose-limiting toxicities occurred in two of two patients at DL5 (G4 thrombocytopenia, G3 lethargy), defined as the maximum tolerated dose and one of six patients at DL4 (G3 lethargy). DL4 was expanded. There were 2 of 27 partial responses and 14 of 27 stable disease [disease control 52%, 95% confidence interval (CI) 32% to 71%]. Median progression-free survival and overall survival were 4.6 (95% CI 2.1–7.0) and 5.6 months (95% CI 2.5–8.7), respectively.

Conclusion: In gemcitabine-refractory PC, gemcitabine (1000 mg/m²) and oxaliplatin (85 mg/m²) can be safely combined with imatinib given on a 7 days on and 7 days off intermittent schedule.

Key words: adenocarcinoma, gemcitabine, gemcitabine-refractory, imatinib, oxalipaltin, pancreatic

introduction

Pancreatic adenocarcinoma is a lethal chemoresistant disease associated with a dismal 5-year survival rate of 6% [1]. The majority of patients have documented or occult disseminated disease at presentation. Gemcitabine remains a standard of care for the treatment of chemo naive advanced pancreatic cancer (PC) [2]. For patients who develop resistance to gemcitabine but who remain of good performance status (PS), there is currently no standard of care owing to a paucity of level III data. A randomised trial of rubitecan against best supportive care (BSC) failed to show a survival benefit [3] and due to poor accrual, the CONKO-003 randomised trial of oxaliplatin/fluorouracil against BSC [4] was closed and redesigned with fluorouracil/folinic acid replacing the BSC arm, therein demonstrating superiority for oxaliplatin/fluorouracil over fluorouracil [5]. Other oxaliplatin-based combinations have been assessed and among these, the gemcitabine/oxaliplatin (GemOx) doublet has shown phase II activity associated with amelioration of symptoms in gemcitabine-refractory PC [6]. The notion that only a minority of pancreatic patients can tolerate second-line therapy was challenged by a recent randomised trial of erlotinib plus gemcitabine or capecitabine for untreated patients, in which 51% of patients received prespecified second-line therapy with capecitabine or gemcitabine [7].

Raised tumour interstitial fluid pressure (IFP) is one of several mechanisms that may contribute to chemoresistance in pancreatic and other solid tumours by impeding transcapillary transport and efficient uptake of therapeutic agents [8]. The pathogenesis of tumour-related raised IFP has not been fully elucidated but involves all tumour compartments including the stroma and supporting vasculature. Stromal platelet-derived growth factor receptor-β (PDGFR-β) may contribute to the modulation of IFP, governed primarily by the paracrine stimulation of stromal fibroblasts resulting in contracture of the interstitium [9]. Platelet-derived growth factor (PDGF)
signalling is also implicated in the autocrine growth stimulation of tumour cells and promotion of angiogenesis [9].

Imatinib is a tyrosine kinase (TK) inhibitor with potent anti-PDGFR-B and anti-c-kit activity, and is licensed for the treatment of gastrointestinal (GI) stromal tumours and chronic myeloid leukaemia. In one body of preclinical experimentation, antagonism of PDGFR-β with imatinib mesylate reduced tumour-related IFP [10] and enhanced the uptake and efficacy of concomitantly administered chemotherapeutic drugs, while showing no activity for imatinib alone [11, 12] leading the authors to propose PDGFR-β targeting as a strategy to improve chemotherapeutic efficiency [13]. This may be particularly relevant in PC, which is often characterised by dense stromal reactions. In preclinical models of PC, imatinib showed limited single-agent antitumour activity [14, 15], enhanced the antitumour effect of gemcitabine [15] and increased the uptake of therapeutic agents including a radioimmunotherapy regimen [16]. Consistent with preclinical observations, imatinib does not appear to have single-agent clinical activity in PC [17, 18]. It has increasingly been evaluated in combination with chemotherapy in a range of solid tumours [19–22]. Early reports indicated considerable toxicity when imatinib was administered on a continuous daily schedule in combination with chemotherapy including dose-limiting myelotoxicity and fatigue when given with low doses of gemcitabine in chemorefractory solid tumours [23]. Intermittent imatinib dose scheduling may increase the feasibility of a combinatorial approach.

The primary objective of this dose escalation study was to determine the safety, feasibility, dose-limiting toxicities (DLTs) and thus, maximum tolerated doses (MTDs) of the combination of GemOx chemotherapy with intermittently administered imatinib in patients with gemcitabine-refractory PC.

**methods**

**patients**

Eligibility criteria included age ≥18 years; locally advanced (LA) or metastatic gemcitabine-refractory PC (progression during or <6 months of previous gemcitabine treatment including adjuvant therapy); Eastern Cooperative Oncology Group PS of zero to one; adequate bone marrow/renal function; serum aspartate aminotransferase <2× upper limit of normal (ULN) (or <5× ULN if liver metastases present) and a life expectancy of >10 weeks. Measurable disease was not obligatory. Exclusion criteria included uncontrolled medical conditions; chemotherapy or investigational drugs within 4 weeks; prior radiation; peripheral neuropathy; criteria included uncontrolled medical conditions; chemotherapy or expectancy of normal (ULN) (or >5× ULN if liver metastases present). All patients provided written informed consent. The study was approved by the local Scientific Review and Research Ethics Committees (CCR 2731) and was conducted in accordance with International Conference on Harmonization and Good Clinical Practice guidelines.

**study design and treatment**

This single centre, open-label, phase I study employed a 3 × 3 dose escalation design [24] to determine the MTDs and overall safety/tolerability of gemcitabine and oxaliplatin in the GemOx doublet when combined with intermittently administered fixed-dose imatinib. Gemcitabine was administered i.v. over 30 min on day 1 and oxaliplatin was administered i.v. over 2 h on day 2 of a two weekly cycle. Standard antiemetics were given. Imatinib, at a fixed dose of 400 mg/day, was given orally on an intermittent 7 days on treatment and 7 days off treatment (7/7) schedule starting 2 days before day 1 gemcitabine and including days 1 and 2 of i.v. chemotherapy. Dose escalation in sequential dose levels (DLs) was mainly of gemcitabine with one dose escalation step for oxaliplatin (Table 1).

DL cohorts comprised three or more patients assessable for DLT in the first 4 weeks (2 cycles), expanding to six patients if one DLT occurred. Dose escalation proceeded to the subsequent DL in the absence of DLT in three patients or less than or equal to one DLT among six patients. The MTD of gemcitabine and oxaliplatin in the three-drug regimen was that which induced DLT in at least two of a maximum of six patients thereby terminating accrual to that DL. The DL below the MTD could be expanded by up to six patients and declared the recommended dose for possible further evaluation (if associated with less than or equal to one DLT among six patients). Patients not assessable for DLT in the first 4 weeks for reasons other than toxicity were replaced.

DLTs were febrile neutropenia, absolute neutrophil count (ANC) <0.5 × 10⁹/l lasting >7 days without fever; platelet count <25 × 10⁹/l; grade 3/4 diarrhoea despite aggressive anti-diarrhoeal therapy; other non-haematological toxicity ≥grade 3 (excluding alopecia, nausea/vomiting and transient elevation of liver enzymes) and sensory neuropathy >grade 2 lasting >7 days. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Next cycle treatment required ANC ≥1.5 × 10⁹/l, platelets ≥100 × 10⁹/l and resolution of any non-haematological toxicities to ≤grade 1, otherwise treatment was delayed with a maximum allowable delay of 4 weeks. Grade 3/4 toxic effects attributable to gemcitabine resulted in dose de-escalation to the next lower DL. Oxaliplatin was reduced from 85 to 65 mg/m² in the event of grade 2 sensory neuropathy >7 days and discontinued for grade 3 neuropathy. Oxaliplatin infusions were lengthened from 2 to 6 h if laryngeal dysaethesia occurred. Grade 3/4 toxic effects attributable to imatinib resulted in subsequent reduction of duration of dosing from 7 to 5 days (starting the day before gemcitabine). Treatment continued for 12 cycles (or longer in patients deriving clinical benefit) unless unacceptable toxicity, progressive disease or consent withdrawal occurred.

**patient evaluation**

Screening included a clinical history, physical examination, full blood count, biochemistry panel, coagulation and electrocardiogram. At every treatment visit, toxicity and standard laboratory panels were assessed, with additional full blood counts (FBCs) on days 4, 8 and 11 of cycles 1 and 2. CA 19–9 was recorded on day 1 of every other cycle. Tumour response was evaluated by computed tomography of the chest/abdomen/pelvis (RECIST guidelines [25]) at baseline (within 28 days of starting protocol therapy) and thereafter every 8 weeks. Responses were confirmed at least 4 weeks after responding scans.

**study end points and objectives**

The primary objective was to determine the MTD of gemcitabine and oxaliplatin in the GemOx doublet when combined with intermittently administered imatinib based on the end point of DLTs in the first

**Table 1. Dose escalation schedule**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Gemcitabine dose (mg/m²)</th>
<th>Oxaliplatin dose (mg/m²)</th>
<th>Imatinib dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
<td>85</td>
<td>400</td>
</tr>
<tr>
<td>1 (starting)</td>
<td>400</td>
<td>85</td>
<td>400</td>
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<tr>
<td>2</td>
<td>600</td>
<td>85</td>
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<tr>
<td>3</td>
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<td>400</td>
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<tr>
<td>5</td>
<td>1000</td>
<td>100</td>
<td>400</td>
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2 cycles (4 weeks). Objective response rates, overall survival (OS) and progression-free survival (PFS) were secondary end points in the intention-to-treat (ITT) population. Survival was calculated from the date of study registration to the date of death (OS) or progression/death (PFS) using Kaplan–Meier with patients censored at the date of last follow-up if still alive.

results

patients

Twenty-seven patients were enrolled between June 2006 and March 2010. The database was analysed in May 2010 after the final patient had completed their DLT assessment period (4 weeks). Patient characteristics are shown in Table 2; 63% of patients were male and the majority of patients were of PS zero or one (96%) with metastatic disease (89%). All patients were gemcitabine-refractory, 40% having previously received gemcitabine in a cytotoxic doublet with capecitabine or cisplatin and 22% having received adjuvant gemcitabine-based therapy. Of the 27 patients, 4 were non-assessable for DLT (DL2 n = 1, DL4 n = 3) due to disease-related deterioration in cycles 1/2 and were replaced in their respective cohorts. All 27 patients were assessable for safety and efficacy in the ITT population. The median time from the final cycle of previous chemotherapy to study registration was 59 days (20–265 days).

<table>
<thead>
<tr>
<th>Table 2. Patient characteristics</th>
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<tbody>
<tr>
<td>All patients (ITT), N = 27a (%)</td>
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<tr>
<td>Median age in years (range)</td>
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<tr>
<td>Male:Female, n (%)</td>
</tr>
<tr>
<td>Site of primary, n (%)</td>
</tr>
<tr>
<td>Body/tail</td>
</tr>
<tr>
<td>Complete pancreas</td>
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<tr>
<td>Head</td>
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<tr>
<td>Performance status, n (%)</td>
</tr>
<tr>
<td>0/1</td>
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<tr>
<td>2</td>
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<tr>
<td>Disease extent, n (%)</td>
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<tr>
<td>Primary/locally advanced</td>
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<tr>
<td>Metastatic</td>
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<tr>
<td>Previous treatmentb, n (%)</td>
</tr>
<tr>
<td>GEM alone</td>
</tr>
<tr>
<td>GEM-CAP or GEM-CIS</td>
</tr>
<tr>
<td>GEM or GEM-CAP + biological agentd</td>
</tr>
</tbody>
</table>

aFour patients were non-evaluable for DLT (DL2 n = 1, DL4 n = 3; disease-related deterioration in cycle 1).
bSix patients had progressed during/after adjuvant therapy (gemcitabine n = 4, gemcitabine + cisplatin n = 1, gemcitabine + erlotinib n = 1).
cGemcitabine + capecitabine or gemcitabine + cisplatin.
dBiological agents included erlotinib, bevacizumab and telovac vaccine (in previous trial protocols).

DLT and MTD

No DLTs were observed in each of the three patients recruited to DLs 1, 2 or 3. One additional patient was recruited to DL2 (n = 4) to replace a patient non-assessable for DLT. At DL4, there was one DLT observed among six patients (G3 lethargy). At DL3, two DLTs occurred in the two recruited patients (G4 thrombocytopenia, G3 lethargy). DL5 was declared the MTD. DL4 was expanded to 15 patients in total including 3 replacement patients with no further DLTs. DL4 was therefore recommended as the dose for further evaluation.

safety

Thrombocytopenia (all grades) was the most frequent haematological toxicity across all DLs (Table 3). Grade 3/4 thrombocytopenia occurred in 1 of 2 patients at DL5 and was observed in 3 of 15 (20%) patients at the recommended DL4 (grade 1/2 = 80%). At DL4, grade 3/4 neutropenia was observed in only 13% of patients. Lethargy was one of the most frequent non-haematological toxicities across all DLs. Grade 3/4 lethargy was observed in 1 of 2 patients at DL5 and in 6 of 15 (40%) patients at DL4. At DL4, non-haematological grade 3/4 toxic effects with frequencies >10% included nausea/vomiting (20%), infection (13%) and lethargy (40%). Grade 2 peripheral neuropathy was seen in 2 of 15 (13%) patients with no cases of grade 3/4 peripheral neuropathy. One patient at each DL experienced oedema.

Treatment-related serious adverse events were observed in 10 patients including infection with normal ANC n = 6; febrile neutropenia n = 2; vomiting n = 4; fever n = 3; atrial flutter n = 1; abdominal pain n = 1; constipation n = 1 and hyperglycemia n = 1. There was one suspected unexpected serious adverse reaction (GI bleeding and renal failure secondary to disease-related thrombosis and anticoagulation) leading to death.

Treatment delivery

A total of 168 cycles of treatment has been given to 27 patients. The median number of cycles administered was 4 (range 1–24). Two patients continue on protocol therapy. Four patients continued beyond 12 cycles. Reasons for discontinuing treatment included documented progressive disease (n = 15), clinical progressive disease (n = 2), patient request (n = 4), toxicity (n = 3) and treatment delay >4 weeks (n = 1).

efficacy

Twenty-four patients have died. Median follow-up for the three surviving patients is 7.3 months (range 1.9–8.4). Median OS (Figure 1) for all patients was 5.6 months [95% confidence interval (CI) 2.5–8.7] and 1-year survival was 28.1% (95% CI 12.1% to 46.6%). PFS (Figure 2) for all patients was 4.6 months (95% CI 2.1–7.0) with a 1-year PFS of 10.7% (95% CI 2.0% to 27.9%). For tumour response, six patients had died and/or were not evaluable. The objective response rate (unconfirmed) was 2 of 27 (7%, 95% CI 1% to 24%) with a disease control rate of 52% (95% CI 32 to 71%). Both partial responses were observed at DL4 and in patients with LA disease, one of which comprised a very bulky primary tumour (initially measuring 13.7 cm and reducing to 7.8 cm). Seven of 27 patients (27%) had progressive
disease. In a prespecified analysis of CA 19-9 trends, no patients achieved a 50% reduction in CA 19-9 levels by 8 weeks.

**discussion**

Based on the hypothesis that PDGFR-β targeting lowers tumour-related IFP and improves chemotherapeutic uptake, our study was designed to examine the safety and feasibility of combining imatinib (400 mg/day) on an intermittent 7/7 schedule with gemcitabine and oxaliplatin in patients with chemorefractory PC. At the toxic DL5, the DLTs were thrombocytopenia and fatigue. At the recommended doses of gemcitabine 1000 mg/m² and oxaliplatin 85 mg/m², one DLT of lethargy was observed among 15 patients (12 assessable for DLT).

At study inception, GemOx appeared to be a promising regimen for the first-line treatment of PC and appeared to be active in the second-line setting [6] leading to its selection for this study, although gemcitabine was not given at a fixed-dose rate (greater potential for myelosuppression). Subsequently, however, a randomised trial failed to report a significant improvement in survival for first-line GemOx compared with gemcitabine alone [26]. Nonetheless, platinum-based combination treatments are often used for treating PC [27].

We chose not to investigate imatinib doses >400 mg/day because of the toxicity observed when this dose was given on a daily schedule. Hence, we sought to lessen toxicity and optimise chemotherapy doses with an intermittent 7/7 scheduling of the 400 mg/day imatinib dose. In a phase I study of patients with chemorefractory solid tumours treated with imatinib at doses of 300 or 400 mg/day continuously in combination with gemcitabine at doses of 700 or 800 mg/m² on days 1, 8 and 15, four of seven patients experienced DLTs (neutropenia n = 2, thrombocytopenia n = 1, fatigue n = 1) leading to early termination of the study [23]. Neutropenia was not dose limiting when imatinib was administered intermittently in our study but dose-limiting thrombocytopenia and lethargy were evident at the MTD (toxic dose) upon increasing the dose of oxaliplatin.

Since the initiation of our trial, two other phase I trials have been published examining the safety and feasibility of combining intermittent imatinib and chemotherapy [28, 29]. In these studies, imatinib was scheduled to straddle chemotherapy delivery to potentially optimise chemotherapy...
uptake and also because single-agent activity was not anticipated. In one study, 30 patients with GI malignancies (17 with PC) were assigned to escalating doses of imatinib (300–700 mg/day) for 8 days, starting 4 days before fixed-dose biweekly fluorouracil/leucovorin; DLTs of severe neutropenia, central fluid retention and nausea were observed at the 700 mg/day imatinib dose and there were no significant pharmacokinetic (PK) interactions [28]. In the other study, an intermittent imatinib schedule was employed after the demonstration of excessive toxicity when imatinib 300 mg/day was combined with gemcitabine 600 mg/m² on days 1, 8 and 15 in 54 patients with chemorefractory solid tumours (10 patients with PC) [29]. Imatinib 400 mg/day was given for 5 days, starting 2 days before every gemcitabine administration with no demonstration of DLT (maximum gemcitabine dose of 1500 mg/m²) or PK drug–drug interactions.

In our study, the target dose of gemcitabine (1000 mg/m²) was deliverable with intermittent imatinib but escalation to the target dose of oxaliplatin (100 mg/m²) was not feasible. PK analysis was not carried out since the drugs assessed are not metabolised by common pathways and drug interactions were not anticipated as supported above. The decision to start imatinib at least 2 days before chemotherapy is supported by preclinical data; in a mouse model of anaplastic thyroid tumours treated with the epothilone EPO906 combined with imatinib, EPO906 uptake was maximal when imatinib was started 2 days before and continued on the day of chemotherapy [12].

The addition of imatinib to GemOx at the recommended DL was well tolerated. Importantly, the rate of grade 3/4 neutropenia was only 13% compared with 8%–12% with GemOx alone in studies of pretreated [6] and chemonaive PC patients [26]. No cases of grade 3 peripheral neuropathy were observed compared with 10% [26] to 12% [6] patients treated with GemOx alone and may reflect the lower dose of oxaliplatin used (85 mg/m²) in our study. However, grade 3/4 nausea (20%) and lethargy (40%) are higher compared with the 0%–6% observed with GemOx alone [6, 26]. Fluid retention, particularly periorbital and leg oedema, is a well-recognised toxicity of patients including one patient (bile duct cancer) with dose-limiting non-cardiac fluid retention. However, dose escalation in that study encompassed higher doses of imatinib up to 700 mg/day, with a recommended dose of 600 mg/day in combination with chemotherapy. In our study, grade 1/2 fluid retention was observed in fewer patients (18.5% of all patients) using the 400 mg/day imatinib dose.

The assessment of efficacy was a secondary objective. The median OS and PFS were 5.6 and 4.6 months, respectively, with an overall response rate and disease control of 7% and 52%, respectively. The survival appears to be better than the median OS of 2.3 and 3.1 months associated with BSC in the two unpublished randomised trials in patients with chemorefractory PC [3, 4]. The results are also comparable to the efficacy associated with single-agent gemcitabine in the first-line treatment of PC, which is noteworthy given that patients were refractory to previous gemcitabine treatment (median time since completion of previous gemcitabine was 59 days). The patients in this study, however, represent a highly selected group with good PS, a well-recognised favourable prognostic variable [32–34] and a relatively uncommon scenario for pretreated PC. Any potential efficacy increment attributable to imatinib cannot be gauged from this single-arm study. Compared with a median OS and PFS of 6 and 4.5 months, respectively, in a phase II study of GemOx alone in patients with chemorefractory PC [6], and accepting the limitations of cross study comparison, the results of our study with the addition of imatinib appear to be similar and not superior.

The most marked responses to treatment were observed in patients with bulky LA tumours. This interesting observation may have a plausible biological basis; in a preclinical model of desmoplastic breast cancer, carcinoma-secreted PDGF appeared to be the main driver of tumour desmoplasia [35], PC, particularly LA disease, is similarly characterised by dense stromal desmoplastic reactions with a complex composition, in which myofibroblastic pancreatic stellate cells appear to have a crucial role and are strongly stimulated by PDGF [36, 37]. The observations in our study may be a chance finding or could reflect an inhibitory effect of imatinib on PDGF signalling in LA tumours, which could potentially relate to reduction in stromal IFP and increased uptake of chemotherapy.

In summary, we explored a novel stromally targeted strategy for patients with chemorefractory PC and demonstrated the safety of administering full-dose gemcitabine but slightly reduced-dose oxaliplatin with intermittent imatinib straddling the chemotherapy administration period. This knowledge could be exploited for future experimental application given that gemcitabine forms the mainstay of treatment of PC. An important avenue for investigation would be to provide in vivo evidence of increased tumour cytotoxic drug uptake in the presence of imatinib in patients with LA PC, thereby potentially providing proof-of-principle validation for targeting PDGFR-β-mediated IFP regulation as a rational therapeutic approach in these patients. 19-F magnetic resonance spectroscopic imaging, suitable for fluorinated compounds such as gemcitabine, is a non-invasive modality used to evaluate tumour drug uptake in humans [38]. To our knowledge, limited clinical functional imaging studies have been published in relation to imatinib PDGFR-β targeting and would be of biological interest, particularly in LA pancreatic tumours.

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references