Background

The incidence of pancreatic cancer in the UK is 9.4/100,000. It is the fifth leading cause of cancer death in the UK and has a grim prognosis, with 5 year survival of only 3%. Approximately 82% of people diagnosed with pancreatic cancer will die within a year as most have late stage disease at the time of diagnosis.\(^1\) Patients with metastatic disease survive 3 to 6 months dependent on the extent of the disease and performance status.\(^2\) In 2008, 8085 people were newly diagnosed with pancreatic cancer in the UK and 8047 people died from the disease in 2009. There has been no improvement in the UK mortality rate for pancreatic cancer since 1955.\(^1\)

As the majority of cases are diagnosed at advanced stages, palliative care will often be the best that can be offered to relieve symptoms and the outcomes remain poor. Palliative surgery and endoscopic placement of biliary drainage stents can be used to control complications such as jaundice and gastric outlet obstruction, and improve quality of life. Alternative treatment options include chemotherapy and radiotherapy.\(^3\)

Gemcitabine has been the standard first line chemotherapy for metastatic pancreatic cancer for many years, on the basis of a phase III trial showing its clinical benefit over fluorouracil; however, the median survival was only 5.6 months and response rate only 5%. Since then, many trials have evaluated gemcitabine as part of doublet or triplet regimens to improve overall outcome. The results from such studies have been largely disappointing.\(^4\)

NICE supports the use of gemcitabine as a treatment option for patients with advanced or metastatic adenocarcinoma of the pancreas and a Karnofsky performance score of ≥ 50, where first line chemotherapy is to be used.\(^3\)

Irinotecan monotherapy and oxaliplatin when combined with fluorouracil have been reported to possess some clinical activity against advanced pancreatic cancer. The combination of oxaliplatin and irinotecan have shown synergistic activity in vitro. A phase I trial combining fluorouracil, leucovorin, irinotecan, and oxaliplatin reported responses in patients with advanced pancreatic cancer. This led to a phase II study of the FOLFIRINOX regimen (oxaliplatin, irinotecan, fluorouracil, and leucovorin) in 46 patients with good performance status and advanced pancreatic cancer; which noted encouraging efficacy and grade 3 or 4 neutropenia in half of these patients. These findings resulted in the initiation of a phase II-III trial to further explore FOLFIRINOX as compared with single agent gemcitabine as first-line treatment in patients with metastatic pancreatic cancer.\(^5\)

Trial data

The FOLFIRINOX study was conducted in France, at 15 centres during phase II and expanded to 48 centres during phase III. It recruited 342 adult patients (median age 61; range 25-76 years) with metastatic pancreatic adenocarcinoma that had not previously been treated with chemotherapy. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and adequate bone marrow and platelet count, liver- and renal function. Exclusion criteria were age ≥ 76 years, endocrine or acinar pancreatic carcinoma, previous radiotherapy, cerebral metastases, history of another major cancer, active infection, chronic diarrhoea, a clinically significant history of cardiac disease, and pregnancy or breast-feeding. The two treatment groups were well balanced but there were fewer measurable target lung metastases in the FOLFIRINOX group than in the gemcitabine group (19.5% vs. 28.7%, \(p = 0.05\)).\(^5\)

Patients were randomised to receive FOLFIRINOX or gemcitabine (GEM) within 1 week after enrollment as follows:
- GEMCITABINE: 1000 mg/m² as 30-minute IV infusion weekly for 7 weeks, followed by a 1-week rest, then weekly for 3 weeks in subsequent 4-week courses.

- FOLFIRINOX: oxaliplatin 85mg/m² as 2-hour IV infusion, immediately followed by leucovorin 400mg/m² as 2-hour IV infusion, with the addition, after 30 minutes, of irinotecan 180mg/m², given as a 90-minute IV infusion. This treatment was immediately followed by fluorouracil 400mg/ m² IV bolus, followed by a continuous IV infusion 2400mg/m² over a 46-hour period every 2 weeks.

Six months of chemotherapy was recommended for patients who had a response. Patients were followed every 3 months until death. In the event of predefined toxic events, protocol-speciﬁed treatment modiﬁcations were permitted: doses of gemcitabine were reduced if the granulocyte or platelet count decreased to pre-specified levels. In case of grade 2, 3, or 4 neutropenia or thrombocytopenia, FOLFIRINOX administration was delayed until recovery and doses were reduced. Filgrastim was not recommended as primary prophylaxis, but it could be considered for high-risk patients.5

Quality of life was assessed with the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30, version 3.0), which was completed every 2 weeks. Safety assessments were performed before each cycle and tumours were measured every 2 months. Patients discontinued the study in the event of unacceptable toxic effects or evidence of progressive disease, or at their request.5

The primary efficacy end point for the phase II analysis was tumour response, and the secondary end point was safety. The trial was planned to continue as a phase III study if >11 responses were observed in the first 40 patients who were randomised to the FOLFIRINOX group. Patients from the phase II analysis were included in the phase III analysis, the primary end point of which was overall survival, and secondary end points were progression-free survival, tumour response, safety, and quality of life.5

The median number of treatment cycles administered was 10 (range, 1 to 47) in the FOLFIRINOX group and 6 (range, 1 to 26) in the gemcitabine group (p<0.001). The median duration of follow-up of 26.6 months. More patients in the gemcitabine group had disease progression before 12 cycles (6 months) (79.9%, vs. 54.6% in the FOLFIRINOX group; p<0.001). The median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, 78%, and 100%, respectively.5

The intention-to-treat population included 171 patients in each group, and the safety population (all patients who received treatment) included 167 patients in the FOLFIRINOX group and 169 patients in the gemcitabine Group. The following findings were noted:5

Survival
- Median overall survival was 11.1 months in the FOLFIRINOX group vs. 6.8 months in the gemcitabine group (hazard ratio for death, 0.57; 95% CI, 0.45 to 0.73; p<0.001).

- Overall survival rates at 6, 12, and 18 months were 75.9%, 48.4%, and 18.6%, respectively, in the FOLFIRINOX group as compared with 57.6%, 20.6%, and 6.0%, respectively, in the gemcitabine group.

- Progression-free survival rates at 6, 12, and 18 months were 52.8%, 12.1%, and 3.3%, respectively, in the FOLFIRINOX group as compared with 17.2%, 3.5%, and 0%, respectively, in the gemcitabine group.
• Median progression-free survival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (hazard ratio for disease progression, 0.47; 0.37 to 0.59; p<0.001).

• Synchronous metastases, a low baseline albumin level (<3.5 g/dl), hepatic metastases, and age > 65 years were identified as independent adverse prognostic factors for overall survival.

• The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (p<0.001).

• Second-line therapy was administered in 80 patients in the FOLFIRINOX group and in 85 patients in the gemcitabine group; no difference in median survival was noted between the groups (4.4 months in each group) from the introduction of second-line therapy.

Adverse events
• Two patients died from treatment-related cause: one from febrile neutropenia in the FOLFIRINOX group and one from cardiac decompensation in the gemcitabine group.

• More adverse events were noted in the FOLFIRINOX group: incidences of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhoea, and sensory neuropathy were significantly higher in the FOLFIRINOX group, whereas the incidence of grade 3 or 4 elevated alanine aminotransferase levels was significantly higher in the gemcitabine group (see table taken from trial paper).

• Grade 2 alopecia occurred in 11.4% of patients in the FOLFIRINOX group vs. 1.2% of patients in the gemcitabine group (p <0.001).

• Filgrastim was administered in 42.5% of patients who received FOLFIRINOX and in 5.3% of patients who received gemcitabine (p<0.001).

• No cholangitis was observed in either group.

<table>
<thead>
<tr>
<th>Event</th>
<th>FOLFIRINOX (N=171)</th>
<th>Gemcitabine (N=171)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = of patients/total no. (%)</td>
<td>n = of patients/total no. (%)</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>75/164 (45.7)</td>
<td>35/167 (21.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9/166 (5.4)</td>
<td>2/169 (1.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15/165 (9.1)</td>
<td>6/168 (3.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Anemia</td>
<td>13/166 (7.8)</td>
<td>10/168 (5.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39/165 (23.6)</td>
<td>30/169 (17.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24/166 (14.5)</td>
<td>14/169 (8.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21/165 (12.7)</td>
<td>3/169 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>15/166 (9.0)</td>
<td>0/169</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated level of alanine aminotransferase</td>
<td>12/165 (7.3)</td>
<td>35/168 (20.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>11/166 (6.6)</td>
<td>7/169 (4.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Quality of life

Despite the higher incidence of adverse events associated with the FOLFIRINOX regimen, a significant increase in the time to definitive deterioration of quality of life was observed in the FOLFIRINOX group as compared with the gemcitabine group.\(^5\) This is presumed to be due to a delay in disease progression that was associated with this treatment arm.\(^6\) At 6 months, 31\% of the patients in the FOLFIRINOX group had a definitive decrease in the scores on the Global Health Status and Quality of Life scale vs. 66\% in the gemcitabine group (hazard ratio, 0.47; 95\% CI, 0.30 to 0.70; \(p<0.001\)). Significant increases in the time until definitive deterioration in the quality of life were also noted in the FOLFIRINOX group for all functional and symptom scales and with respect to appetite loss, dyspnoea, and constipation. Time to a definitive decrease in the scores that were associated with diarrhoea, insomnia, or financial difficulties caused by a physical condition or medical treatment did not differ significantly between regimens.\(^5\) These data are valuable in assessing the risk/benefit ratio of any new therapeutic option, given patients’ short survival duration and the pain, anorexia, and inanition that so often accompanies the underlying disease process.\(^6\)

Based on the study findings, the National Comprehensive Cancer Network in the US in 2011 added FOLFIRINOX as a category 1 recommendation (based upon high level evidence and uniform consensus among panel that the intervention is appropriate) for first line treatment of good performance status patients with metastatic disease, but acknowledging concerns about toxicity.\(^7\)

Drug costs for 6 cycles (based on average body surface area 1.73m\(^2\))\(^8,9\)

Six months (24 weeks) of chemotherapy for BSA 1.73/m\(^2\) USING BNF 62 prices

GEMCITABINE (1000 mg/m\(^2\) weekly for 7 weeks, followed by 1-week rest, then weekly for 3 weeks in subsequent 4-week courses):

\[
1000mg \times 1.73 = 1730mg \times 7 = -12,110mg \text{ (equiv to 2 cycles = 8 wks)} + \\
1730mg \times 12 \text{ (12 infusions over remaining 4 cycles) = 20,760mg}
\]

\[
2g = £324; 1mg = £0.162
\]

6 cycles of 20,760mg x £0.162 = £3363

FOLFIRINOX:

FOLFIROINOX (oxaliplatin 85mg/m\(^2\), leucovorin 400mg/m\(^2\), irinotecan 180mg/m\(^2\), and fluorouracil 400mg/m\(^2\) bolus and IV infusion 2400mg/m\(^2\)) given every 2 weeks = 12 treatments over 6 cycles:

**Oxaliplatin 85 mg/m\(^2\)**

\[
85 \times 1.73 = 147.05mg \times 12 = £1764.60mg
\]

100mg = £299.50, 1mg = £2.995

6 cycles 1764.60mg x £2.995 = £5229

**Leucovorin 400 mg/m\(^2\)**

Calcium folinate = calcium leucovorin

400mg x 1.73 = 692mg, x 12 = 8304mg

350mg = £90.98, 1mg = £0.26

6 cycles 8304mg x £0.26 = £2159.04

**Irinotecan 180 mg/m\(^2\)**

180mg x 1.73 = 311.40mg x 12 = 3736.80mg

500mg = £601.25, 1mg = £1.2025

6 cycles 3736.80mg x £1.2025 = £4493.50
Fluorouracil 400 mg/m2 plus 2400 mg/m2
692mg + 4152mg = 4844mg x 12 = 58,128mg
2500mg = £64, 1mg = £0.0256
6 cycles 58,128mg x £0.0256 = £1488.01

| Total cost 6 cycles FOLFIRINOX = £13,369 |
| Cost 6 cycles GEMCITABINE = £3363 |

Nb: The hospital prices of gemcitabine and FOLFIRINOX may be up to a fifth and a tenth of the above list prices, respectively

Service implications

The administration of FOLFIRINOX involves the infusion of drugs in sequential order, ending with a continuous infusion of fluorouracil over 46 hours (every 2 weeks) compared with a 30 minute infusion of gemcitabine (weekly x 7 weeks then weekly for 3 of 4 weeks thereafter). The complexity of the former regimen and infusional pump therapy has service and cost implications. In addition, the use of growth factor support as primary prophylaxis, which was not mandated in the French trial, but was eventually administered in 42.5% of patients in the FOLFIRINOX arm, may need to be taken into consideration in patients with pre-existing endobiliary stents in whom this regimen is being considered.6

Summary

Currently, FOLFIRINOX is the only combination regimen that has demonstrated a statistical and clinical survival benefit over gemcitabine. The phase III study reported a 4.3 month survival benefit over gemcitabine (11.1 vs. 6.8 months) in the first-line treatment of patients with metastatic pancreatic adenocarcinoma and good ECOG performance status, no cardiac ischaemia, and normal or nearly normal bilirubin levels. However, this was at the expense of increased toxicity, including higher rates of febrile neutropenia.
Points for consideration

Survival benefits vs. toxicity
The principal question arising from these study findings is whether the absolute survival benefit conferred by FOLFIRINOX is clinically meaningful and worth the added risks and toxicities in a palliative setting. Ko et al note that an absolute incremental improvement in median survival of >4 months with FOLFIRINOX is quite striking and substantially exceeds those reported in pivotal trials that led to FDA approval of other cytotoxic and targeted agents. They suggest that in a disease characterised by a median survival of less than 1 year, few would argue that a survival benefit of this magnitude does not justify the added risk, though, they stress that FOLFIRINOX will not be suitable for a lot of patients.6

Are the trial subjects representative of average patient with pancreatic cancer?
The patient-selection criteria in the study were more rigorous than those in previous studies, and only 38% had carcinoma of the pancreatic head. This distribution of tumour location is the opposite of that typically seen in clinical practice. Surveillance data indicate a 3:1 ratio of pancreatic cancers located in the head versus the body or tail. Other multicentre trials of advanced pancreatic cancer similarly report the majority of tumours to arise within the pancreatic head.6 This difference may be related to the exclusion of patients with a high bilirubin level because of the increased risk of irinotecan-induced toxicity, resulting in a low proportion of enrolled patients with biliary stents (14.3%).5 Patients with obstructing pancreatic head lesions and indwelling biliary stents are at risk of infectious complications such as ascending cholangitis and biliary sepsis that could be potentially life threatening in the setting of profound myelosuppression. The FOLFIRINOX regimen, with its 46% rate of grade 3 to 4 neutropenia, could thus prove to be a difficult regimen to administer in such patients, particularly in centres and locations where access to specialists for the endoscopic management of biliary complications may be limited.6

Toxicity profile of FOLFIRINOX in non-French populations
Previous analyses have demonstrated that the tolerability of fluoropyrimidines may differ by region, with East Asian patients experiencing the fewest and patients in the US experiencing the most adverse effects. Subgroup analysis of North Central Cancer Trials group 9741, a large colorectal cancer trial that evaluated several combination regimens that contained the same components as FOLFIRINOX, found significant differences in severe adverse event rates between white and black patients, likely reflecting marked racial differences in relevant pharmacogenetics. Thus, it would be useful to assess how well FOLFIRINOX is tolerated among different ethnicities and geographic regions.6

Data not reported in trial paper
Other data not reported in the clinical trial paper which might aid the decision to use the FOLFIRINOX regimen include data on the frequency of less severe (grade 1 or 2) toxicities and hospitalisation rates, as well as data on practical considerations, such as the minor inconvenience associated with infusional pump therapy and central catheters.6

References

8. MIMS January 2012
9. BNF Sept 2011 (no 62)

Details of search strategy:

NeLM
ASCO
NICE
NCCN

Embase/Medline:
Search History:
1. EMBASE; FOLFIRINOX.ti,ab; 38 results.
2. EMBASE; exp PANCREAS TUMOR/; 67890 results.
3. EMBASE; 1 AND 2; 27 results.
4. EMBASE; 3 [Limit to: Human and English Language]; 19 results.
5. EMBASE; exp FLUOROURACIL/ [Limit to: Human and English Language]; 57493 results.
6. EMBASE; exp IRINOTECAN/ [Limit to: Human and English Language]; 14360 results.
7. EMBASE; exp OXALIPLATIN/ [Limit to: Human and English Language]; 10884 results.
8. EMBASE; 2 AND 5 AND 6 AND 7 [Limit to: Human and English Language]; 604 results.
9. EMBASE; exp PHASE 3 CLINICAL TRIAL/ OR exp PHASE 4 CLINICAL TRIAL/ OR exp CONTROLLED CLINICAL TRIAL [+NT]/; 333476 results.
10. EMBASE; 8 AND 9 [Limit to: Human and English Language]; 48 results.
11. EMBASE; 4 OR 10 [Limit to: Human and English Language]; 66 results.
12. MEDLINE; FOLFIRINOX.ti,ab; 22 results.
13. MEDLINE; exp PANCREATIC NEOPLASMS/; 49555 results.
14. MEDLINE; 12 AND 13 [Limit to: Humans and English Language]; 12 results.
15. MEDLINE; exp FLUOROURACIL/ [Limit to: Humans and English Language]; 21595 results.
16. MEDLINE; IRINOTECAN.ti,ab; 4959 results.
17. MEDLINE; OXALIPLATIN.ti,ab; 4075 results.
18. MEDLINE; 13 AND 15 AND 16 AND 17 [Limit to: Humans and English Language]; 17 results.
19. MEDLINE; 14 OR 18 [Limit to: Humans and English Language]; 26 results.
20. EMBASE,MEDLINE; Duplicate filtered: [4 OR 10 [Limit to: Human and English Language]], [14 OR 18 [Limit to: Humans and English Language]]; 92 results.