Spotlight

Combination or single-agent chemotherapy as adjuvant treatment for pancreatic cancer?

TC and JVL declare no competing interests

For more on **CONKO-001** see *JAMA* 2013; **310:** 1473–81

For more on **ESPAC-3** see 2012; **308:** 147–56 and **Articles** *Lancet* 2017; **389:** 1011–24

For more on **JASPAC 01** see **Articles** *Lancet* 2016; **388:** 248–57

For more on **ESPAC-4** see **Articles** *Lancet* 2017; **389:** 1011–24

For more on the **PRODIGE 24 trial** see *N Engl J Med* 2018; **379:** 2395–406

For more on the **evolution of adjuvant therapy for pancreatic cancer** see *Ann Onc* 2015; **26** (suppl 5): v56–v68

For more on **molecular stratification for pancreatic cancer** see *Gastroenterology* 2018; published online Aug 27. DOI:10.1053/j.gastro.2018.08.033

Opening opinion: combination chemotherapy

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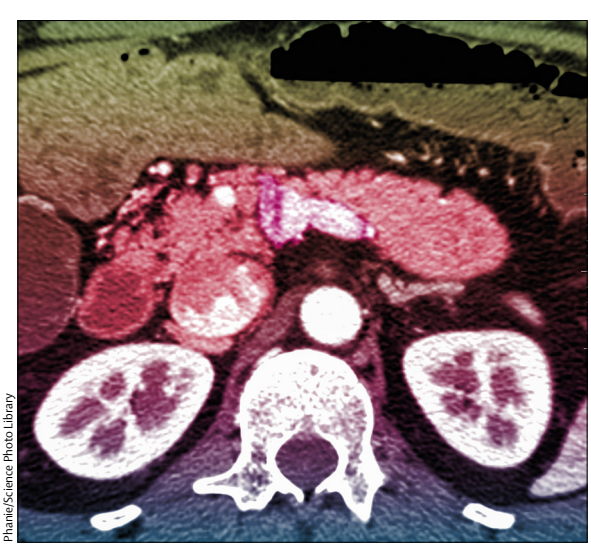
Combination chemotherapy is now the standard adjuvant treatment for patients with resected pancreatic cancer, because single-agent therapies still prove disappointing; in single-agent trials, between 71% and 78% of patients relapse within 2 years. Until recently, six cycles of single agent gemcitabine was the standard of care in patients with pancreatic cancer after complete tumour resection following the CONKO-001 trial, in which 5-year overall survival doubled in patients treated with gemcitabine (20·7% [95% CI 14·7–26·6]) compared with observation (10·4% [5·9–15·0]). The ESPAC-3 trial compared 5-fluorouracil plus folinic acid versus gemcitabine; 5-year overall survival was 15·9% (95% CI 12·7–19·4) and 17·5% (14·0–21·2), respectively. In the Japanese study JASPAC 01, S-1 improved 5-year overall survival compared with gemcitabine (44·1% [95% CI 36·9–51·1] *vs* 24·4% [18·6–30·8]), but additional clinical trials are needed to assess the efficacy of S-1 in non-Asian patients. Unfortunately, the combination of gemcitabine with erlotinib or sorafenib did not improve overall survival in the CONKO-004 (NCT00785421) and CONKO-005 (EudraCT 2007-003813-15) trials.

The first practice-changing combination therapy trial in this setting was ESPAC-4, which assigned 722 patients who underwent resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection) to adjuvant gemcitabine or gemcitabine plus capecitabine, irrespective of postoperative CA19-9 values. At a median follow-up of 43·2 months, the combination therapy significantly improved overall survival, which was 28·0 months (95% CI 23·5–31·5) in the gemcitabine plus capecitabine group versus 25·5 months (95% CI 22·7–27·9) in the gemcitabine group. Subgroup analysis showed a significant benefit for gemcitabine plus capecitabine compared with gemcitabine alone in male patients, those with R0 resection, tumours less than 30 mm, postoperative CA19-9 levels greater than 92·5 KU/L, venous resection, and local invasion. Toxicity was higher with combination therapy, especially grade 3–4 neutropenia, diarrhoea, and hand-foot syndrome. There were no differences in quality of life between treatment groups as per the EORTC QLQ-C30 questionnaire. The ASCO and ESMO guidelines have, since 2017, recommended this doublet regimen in the absence of concerns about toxicity or tolerance.



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The PRODIGE24 trial compared a modified FOLFIRINOX regimen with no bolus 5-fluorouracil and 150–180 mg/m² dose of irinotecan (mFOLFIRINOX) with gemcitabine alone as adjuvant chemotherapy in 493 patients. Eligible patients were 18–79 years old, had pancreatic ductal adenocarcinoma resected (R0 or R1 resection) within 12 weeks of randomisation, and serum CA19-9 concentrations up to 180 U/mL. At a median follow-up of 33·6 months, median disease-free survival (primary endpoint) was 21·6 months (95% CI 17·7–27·6) in the mFOLFIRINOX group and 12·8 months (11·7–15·2) in the gemcitabine group. Median overall survival was 54·4 months (95% CI 41·8–not reached) in the mFOLFIRINOX group and 35·0 months (28·7–43·9) in the gemcitabine group. To my knowledge, these results are the best to date for adjuvant treatment of resectable pancreatic cancer.

Although not powered, subgroup analyses showed that the benefit in disease-free survival in patients who received combination therapy was significant irrespective of gender, tumour location, status of surgical margins, age younger than 65 years or 65 years or older, and treatment duration. The disease-free survival benefit was also observed both in favourable prognostic subgroups (<70 years, well or moderately differentiated tumours, no venous resection, low CA19-9) and poor prognostic subgroups (T3/T4 stage, positive lymph nodes). However, in the subgroup of older patients (>70 years), there was no obvious advantage of mFOLFIRINOX over gemcitabine in terms of disease-free survival.

Grade 3–4 adverse events occurred in 180 (76%) of 237 patients in the mFOLFIRINOX group and 128 (53%) of 242 patients in the gemcitabine group, but toxicities were manageable. The predominant toxicity was grade 3–4 diarrhoea, which occurred in 44 (18%) of 247 patients treated with modified FOLFIRINOX, with combination therapy.

These results suggest that combination chemotherapy, and particularly the mFOLFIRINOX regimen, should now be the standard of care in fit patients (those with an Eastern Cooperative Oncology Group [ECOG] performance status of 0 or 1, no contraindication to fluoropyrimidines, and no severe postoperative diarrhoea).

Counter opinion: still a place for monotherapy

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The management of patients with pancreatic cancer needs to improve substantially to translate into clinically relevant overall survival benefits. In patients with resectable disease, surgery followed by adjuvant chemotherapy is the standard of care and over the last 20 years a modest but substantial benefit has been achieved. Median overall survival has been improved, from 15–20 months with surgery alone to 23 months with single-agent chemotherapy (5-fluorouracil or gemcitabine). Moreover, the JASPAC 01 trial reported a median overall survival of 46·5 months (95% CI 37·8–63·7) in east Asian patients treated with S1 monotherapy compared with 25·5 months (22·5–29·6) with gemcitabine, although the generalisability of these results remains unknown.

Recently, PRODIGE 24 clearly showed the benefit of the multi-therapy with a modified FOLFIRINOX regimen (mFOLFIRINOX) compared with gemcitabine monotherapy in patients with resectable pancreatic cancer, with emphasis on the huge leap achieved in disease-free survival and overall survival in the mFOLFIRINOX group compared with the gemcitabine group. Beyond these impressive results in PRODIGE 24, the question to address next is: which patients can be still treated with monotherapy? The answer may be relatively easy to find if we look at the eligibility criteria of PRODIGE 24, relatively even more strict than those established in PRODIGE 11 (EudraCT 2009-015785-64) including patients with metastatic disease. In PRODIGE 24, eligible patients were younger than 80 years and had an ECOG performance status of 0–1, no heart disease, no severe comorbidities, no inflammatory bowel, no postoperative bowel disorders, and good recovery after surgery. Additionally, in the adapted mFOLFIRINOX regimen, 5-fluorouracil bolus was excluded and irinotecan was decreased to 150 mg/m^2 to reduce the risk of serious diarrhoea observed with the full-dose regimen, and prophylactic use of granulocyte-colony stimulating factor was allowed to limit febrile neutropenia. Despite these precautions, the toxicity profile of mFOLFIRINOX was marked by a high frequency of grade 3–4 diarrhoea, and less remarkably by fatigue, vomiting, and mucositis, all of which may explain the high proportion of dose reductions and treatment discontinuations in patients treated with mFOLFIRINOX. Although adverse events did not affect overall survival outcomes, patient selection and tolerance concerns with this multi-therapy regimen should prompt clinicians to recommend this new standard of care for very fit patients only and continue to propose alternative adapted therapies for older patients (>70 years old), those with worse ECOG performance status (>1), or those with postoperative complications. For these less fit patients, S-1 monotherapy appears to be a good alternative in terms of safety and efficacy. Additionally, gemcitabine monotherapy has shown good suitability and tolerance with a 10-year overall survival benefit compared with surgery alone. The long-term benefit of gemcitabine monotherapy could be due to the use of additional chemotherapy once recurrence occurs, but also because of a better selection of patients for adjuvant gemcitabine (surgical method, margin evaluation, and application of preoperative and postoperative CA19.9 cutoff values). Additionally, several studies have suggested hENT1 as a predictive biomarker for gemcitabine therapy benefit, although a robust assessment of this biomarker is warranted. Recent findings about molecular stratification of patients with pancreatic cancer will contribute to improve and guide therapeutic choices in the future.

In summary, the choice of adjuvant therapy for patients with resectable pancreatic cancer should rely on the patient (considering age, general health status and nutritional condition, achievement of postoperative recovery without bowel or liver disorders, and personal choice regarding quality of life and administration convenience); the rapidly evolving perioperative setting, with more patients receiving neoadjuvant therapy aimed at downstaging, thus conditioning posterior treatments; and the tumour characteristics influencing the risk of recurrence. Although speculative, molecular profiling and circulating tumour DNA monitoring might allow future stratification and adapted treatment allocation for patients with pancreatic cancer.

In conclusion, mFOLFIRINOX administered cautiously is the more efficacious therapy for patients with resectable pancreatic cancer in the adjuvant setting and the new standard of care for fit patients after surgery; however, gemcitabine or fluoropyrimidine monotherapies remain good alternatives in frail and older patients because of their comparably favourable tolerability. Molecularly-driven patient stratification would probably help clinicians to recommend individualised regimens in the future.