Selected Summaries

ESPAC-4 trial: A summary

Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, Faluyi O, O'Reilly DA, Cunningham D, Wadsley J, Darby S, Meyer T, Gillmore R, Anthoney A, Lind P, Glimelius B, Falk S, Izbicki JR, Middleton GW, Cummins S, Ross PJ, Wasan H, McDonald A, Crosby T, Ma YT, Patel K, Sherriff D, Soomal R, Borg D, Sothi S, Hammel P, Hackert T, Jackson R, Büchler MW for the European Study Group for Pancreatic Cancer. (University of Liverpool, Liverpool, UK; The Royal Liverpool University Hospital, Liverpool, UK; The Clatterbridge Cancer Centre, Wirral, UK; University of Manchester/The Christie NHS Foundation Trust, Manchester, UK; Manchester Royal Infirmary, Manchester, UK; Royal Marsden Hospital, London, UK; Weston Park Hospital, Sheffield, UK; Royal Free Hospital, London, UK; St James's University Hospital, Leeds, UK; Karolinska Institute, Stockholm, Sweden; Clinical Research Sörmland, Eskilstuna, Sweden; University of Uppsala, Uppsala, Sweden; Bristol Haematology and Oncology Centre, Bristol, UK; University of Hamburg Medical institutions UKE, Hamburg, Germany; Royal Surrey County Hospital, Guildford, UK; Guy's Hospital, London, UK; Hammersmith Hospital, London, UK; The Beatson West of Scotland Cancer Centre, Glasgow, UK; Velindre Hospital, Cardiff, UK; Queen Elizabeth Hospital, Birmingham, UK; Churchill Hospital, Oxford, UK; Derriford Hospital, Plymouth, UK; Ipswich Hospital, Ipswich, UK; Skåne University Hospital, Lund, Sweden; University Hospital Coventry, Coventry, UK; Hôpital Beaujon, Clichy, France; University of Heidelberg, Germany.) Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017;**389:**1011–24.

SUMMARY

The authors conducted a large multicentre, phase 3, randomized controlled European trial, in patients with resected carcinoma pancreas, to compare adjuvant gemcitabine alone with a combination of gemcitabine and capecitabine. The respective groups had 366 and 364 randomly assigned patients who received six 4-weekly cycles of either 1000 mg/m^2 gemcitabine (once weekly for 3 weeks) or along with 1660 mg/m^2 oral capecitabine (daily for 3 weeks). The pragmatic design included all patients with complete macroscopic resection (both R0 and R1), and no evidence of metastasis. Patients with prior neoadjuvant therapy, R2 resection or stage IV disease were excluded from the study. The primary end-point was overall survival. With a median overall follow-up of 43.2 months, the median overall survival for the combination chemotherapy group was significantly better than that in the gemcitabine alone group (28 *v.* 25.5 months; p=0.032). Multivariate analysis identified the adjuvant combination (gemcitabine and capecitabine) chemotherapy, resection margin, postoperative CA 19-9, tumour grade, nodal status and tumour size as independent prognostic factors for overall survival.

The authors also compared the results with those in the earlier ESPAC adjuvant trials for pancreatic cancer and showed that combination chemotherapy yields the best survival. In the ESPAC-1 trial, the 5-year survival was 21.1%, 10.8% and 8% for adjuvant chemotherapy (5-fluorouracil [5-FU] and folinic acid), adjuvant chemoradiotherapy and no adjuvant therapy, respectively; in the ESPAC-3 (v2) trial, it was 17.5% and 15.9% for the adjuvant gemcitabine and adjuvant 5-FU and folinic acid, respectively; in the ESPAC-4 trial, it was 16.3% and 28.8% for the adjuvant gemcitabine and adjuvant combined gemcitabine and capecitabine, respectively.

Treatment compliance (six cycles of chemotherapy completed) was moderate (65% and 54% in the gemcitabine alone and combination chemotherapy arms, respectively). Some grade III–IV adverse events were more common in the combination chemotherapy arm (diarrhoea, infections, neutropenia and hand–foot syndrome). However, these adverse events had no effect on the quality of life as was assessed by patient-filled questionnaires (at 3, 6 and 12 months) and did not have any significant difference in the two treatment arms (p=0.3).

However, the median relapse-free survival was similar (13.9 and 13.1 months; p=0.082), and the 5-year relapse-free survival was 18.6% *v.* 11.9%. Patients with disease relapse received additional therapy in 33% of the combination chemotherapy group and 39% of the gemcitabine alone group. Overall relapse rate and the sites of relapse were similar in the two treatment arms.

COMMENT

Pancreatic adenocarcinoma continues to be a disease with a bleak prognosis in most patients. Studies focused on extensive surgery with nodal clearance did not yield any tangible survival benefits and hence the research focus shifted to adjuvant chemotherapy. The ESPAC-1 study, initially, cleared the way for 5-FU/folinic acid as the adjuvant chemotherapy of choice after resection of pancreatic carcinoma.[1] The ESPAC-3 (v2) trial showed that gemcitabine is an alternative to 5-FU with similar survival.[2] Meanwhile, other studies, such as CONKO-001, also corroborated the survival benefit of gemcitabine (as compared to no adjuvant therapy), in patients with resected pancreatic carcinoma.[3]

To increase the efficacy of the adjuvant chemotherapy, several combinations were tried in advanced pancreatic cancer. However, randomized controlled trials in advanced pancreatic carcinoma did not show a clear survival benefit of gemcitabine–cisplatin or gemcitabine–oxaliplatin combinations (as compared to gemcitabine alone).[4,5] FOLFIRINOX combination did show some survival advantage but at the risk of serious adverse events.[6] Cunningham *et al*. showed improvement in survival with the combination of gemcitabine and capecitabine (as compared to gemcitabine alone) in advanced pancreatic carcinoma.[7] This formed the basis of studying the same combination in the adjuvant setting for resected pancreatic carcinoma in the ESPAC-4 trial.

The overall survival clearly improved in this pragmatic trial that included all patients with macroscopic resection (both R0 and R1 resection). It is well recognized that a large number of resections in pancreatic carcinoma are microscopic margin-positive (R1 resection). The ESPAC-4 trial has taken the more accepted definition of R1 resection as any tumour cells within 1 mm of the resection margin as opposed to microscopic residual tumour at the resection margin, which was adopted by the two other relevant trials, i.e. CONKO-001 and JASPAC-1. Accordingly, the proportion of R1 resection is higher in the ESPAC-4 trial as compared to the CONKO-001 or JASPAC-1 trial (60%, 17% and 13%, respectively). It is well recognized that resection margin status is a strong determinant of survival. Although combination chemotherapy showed a marked improvement in overall survival

after R0 resection (median 39.5 months *v.* 27.9 months), there was only a small gain in overall survival in patients with R1 resection (23.7 months *v.* 23.0 months). This underscores the importance of good surgery in achieving negative surgical margins as well as accurate pathological assessment of margin status.

While the statistical benefit of the adjuvant gemcitabine and capecitabine chemotherapy is acknowledged, the fact remains that the absolute benefit of overall survival is about 2.5 months. In addition, both arms of the study have an equivalent relapse rate (66% and 65%) with no difference in the disease-free survival. Despite its gains, the combination chemotherapy does not seem to offer improvement in cure from the disease and the survival gains are modest at best. An analysis by another author has calculated the possible improvement in cure rate of about 3.7% over the control arm and the number needed to treat of 25 patients for the benefit of survival in one patient.[8]

Salvage second-line chemotherapy is gaining importance in pancreatic carcinoma with relapse. In the current trial, 33%–39% patients received salvage chemotherapy after relapse in both arms. Although the pragmatic results of the trial hold true statistically, the effect of this salvage chemotherapy on overall survival has not been addressed in the trial. With the advent of more chemotherapeutic options in specific subsets of patients with pancreatic carcinoma, this question will have more and more impact on assessment of adjuvant trials in the future.

To understand the ESPAC-4 trial better, the results of the Japanese JASPAC trial (2016) should be put in perspective, even though these may not be directly comparable.[9] The JASPAC trial compared adjuvant S-1 to gemcitabine after resection in pancreatic carcinoma. The results of this trial showed a major improvement in overall survival with adjuvant S-1 versus gemcitabine (median survival 46.5 *v.* 25.5 months; 5-year survival 59.7% *v.* 24.4%, respectively). It appears that the JASPAC trial seems to have better risk patients due to the lower R1 resection rate (13%), lower postoperative CA 19-9 levels (increased in 26% *v.* 32% in ESPAC-4), higher proportion of N0 patients (37% *v.* 20% in ESPAC-4) and better performance status (status 0 in 69% *v.* 42% in ESPAC-4). However, it seems unlikely that these differences would explain the large survival advantage gained with S-1. Western authors have doubted the reproducibility of the results of S-1 in western populations, due to racial differences in metabolism. The drug is as yet untested in the Indian subcontinent.

Thus, it seems that in the Indian subcontinent, following the ESPAC-4 trial, the current standard of care for adjuvant therapy after resection for pancreatic carcinoma should be gemcitabine and capecitabine. This also makes practical sense in view of the large experience gained by medical oncologists with these two drugs in Indian patients. However, much more research is needed to further the modest gains in overall survival showed by the ESPAC-4 trial in patients with resected pancreatic carcinoma.

REFERENCES

1 Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, *et al.* Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: A randomised controlled trial. *Lancet* 2001;**358:**1576–85.

2 Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, *et al.* Adjuvant chemotherapy with fluorouracil plus folinic acid vs. gemcitabine following pancreatic cancer resection: A randomized controlled trial. *JAMA* 2010;**304:**1073–81.

3 Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, *et al.* Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: The CONKO-001 randomized trial. *JAMA* 2013;**310:** 1473–81.

4 Colucci G, Labianca R, Di Costanzo F, Gebbia V, Cartenì G, Massidda B, *et al.* Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: The GIP-1 study. *J Clin Oncol* 2010;**28:**1645–51.

5 Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, André T, *et al.* Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005;**23:**3509–16.

6 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, *et al.* FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;**364:**1817–25.

7 Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, *et al.* Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009;**27:**5513–18.

8 Deplanque G, Demartines N. Pancreatic cancer: Are more chemotherapy and surgery needed? *Lancet* 2017;**389:**985–6.

9 Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, *et al.* Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: A phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet* 2016;**388:**248–57.

RAJNEESH KUMAR SINGH
Department of Surgical Gastroenterology
Sanjay Gandhi Postgraduate Institute of Medical Sciences
Lucknow
Uttar Pradesh
rajneeshkumarsingh@hotmail.com