Editorial

Adjuvant chemotherapy with gemcitabine plus erlotinib *vs.* gemcitabine alone for patients with resected pancreatic ductal adenocarcinoma: is there a role for erlotinib?—review of the open label phase III trial CONKO 005

Mathilde Wisniewski, Pierre-Alain Placide, Sandra Granier, Yacoub Al Shatti, Shuaib Al Qalaf, Mohamed Bouattour, Michele Lamuraglia, Pascal Hammel

Department of Digestive and Medical Oncology, Hôpital Beaujon (AP-HP), University Denis Diderot-Paris VII, Clichy, France

Correspondence to: Pascal Hammel. Department of Digestive Oncology, Hôpital Beaujon, 100 boulevard Leclerc, 92110 Clichy, France.
Email: pascal.hammel@aphp.fr.

Provenance: This is an invited Editorial commissioned by Editor-in-Chief Yilei Mao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China).

Comment on: Sinn M, Bahra M, Liersch T, *et al.* CONKO-005: Adjuvant Chemotherapy With Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. J Clin Oncol 2017;35:3330-7.

Submitted Jun 22, 2018. Accepted for publication Aug 07, 2018.
doi: 10.21037/hbsn.2018.08.03
View this article at: http://dx.doi.org/10.21037/hbsn.2018.08.03

Sinn *et al.* (1) report the results of a multicenter trial comparing the combination of gemcitabine and erlotinib with gemcitabine alone for adjuvant therapy in 436 patients who underwent R0 resection for pancreatic ductal carcinoma (PDAC).

PDAC is a devastating disease as less than 10% of patients are still living 5 years after the diagnosis. Surgery offers the single chance of cure, but no more than 15% of patients may achieve a curative-intent resection and most of them relapse within 2 years (2). Adjuvant chemotherapy after surgery is needed to treat an undetectable concomitant micrometastatic disease often present, explaining why 71–76% of patients relapse 1 year after surgery and no more than 20% to 30% are still living at 5 years (2).

Since 2001, adjuvant chemotherapy with 5-fluorouracil (5-FU) and leucovorin (LV) after curative-intent pancreatic resection has been the standard of care for all tumor stages, while the role of adjuvant radiation therapy is still undefined (3,4). The ESPAC 1 trial provided the first robust evidence that 6 months of adjuvant chemotherapy with these drugs improved survival compared to simple observation [median overall survival (OS): 20.1 months in the chemotherapy arm *vs.* 15.5 months in the observation arm, P=0.009] and the chemoradiation arm. The German CONKO-001 trial showed that gemcitabine administration was better than simple observation whether the resected tumor was R0/R1 or N0/N1, doubling disease-free survival (DFS) (13.4 *vs.* 6.9 months, P=0.001) and resulting in longer median OS (22.8 *vs.* 20.2 months, P=0.005 for an estimated 5-year survival of 21% *vs.* 9% (5). Thereafter, the ESPAC 3 trial compared gemcitabine and 5FU/LV, initially with an observation arm that was closed when the mature results of ESPAC-1 were available. Results obtained were similar, with a median OS of 23.6 *vs.* 23 months with gemcitabine and 5-FU/LV [hazard ratio (HR) 0.94, P=0.7], respectively. Grade 3–4 hematological toxicity was higher in the gemcitabine arm (P<0.003) (6). Intra-tumoral expression of the hENT-1 protein was then evaluated as a potential predictive marker for gemcitabine efficacy (7), but this marker is not yet recommended in routine practice due to discordant results and the lack of a validated anti-hENT1 antibody (8).

In the next step, the ESPAC 4 trial has tested the combination of gemcitabine and capecitabine *vs.* gemcitabine alone (9). Grade 3–4 toxicity (neutropenia and hand-foot syndrome) was higher in the combination arm compared to gemcitabine alone (38% *vs.* 24% and a 7% *vs.* 0%, respectively; P<0.001). OS was 28 months

in the experimental arm and 25.5 months in single-gemcitabine arm (HR 0.82; 95% CI, 0.68–0.98, P=0.032). Despite certain limitations [lack of postoperative computed tomography (CT), inclusion of patients with high CA 19.9 serum levels and similar DFS between the two arms], due to the benefit in estimated 5-year OS, i.e., 28.8% (22.9–35.2%) *vs.* 16.3% (10.2–23.7%), gemcitabine plus capecitabine could was considered a new standard in this setting. Meanwhile, the Japanese non-inferiority trial JASPAC-01 reported impressive results in 385 patients with the S-1 compound compared to gemcitabine [5-year OS 44.1% (36.9–51.1%) in the S-1 group *vs.* 24.4% (18.6–30.8%)] (10). However, the S-1 compound has not been tested in Western countries. Finally, the CONKO-006 trial (11) compared the combination of gemcitabine plus sorafenib to placebo in 122 patients who underwent R1 resection and found no difference in disease free survival (DFS) (9.6 *vs.* 10.7 months, P=0.89).

Erlotinib is an oral quinazoline derivative, a potent inhibitor of epidermal growth factor receptor (EGFR) related tyrosine kinase. In 2006, Moore *et al.* (12) reported that gemcitabine plus oral erlotinib 100 or 150 mg daily was weakly but significantly better than gemcitabine alone in patients with advanced PDAC (HR 0.82; 95% CI, 0.69–0.99, P=0.038). These results prompted Sinn *et al.* (1) to test this drug in adjuvant setting. Four hundred and thirty-six patients were randomized between April 2008 and July 2013 in this open-label phase III trial performed in 57 centers in Germany. Patients were stratified according to the usual criteria [surgery, lymph node involvement (N0/N1), and centers] and were randomly assigned (1:1) to receive gemcitabine 1,000 mg/m^2 and daily oral erlotinib 100 mg, or gemcitabine alone. In this study, R0 resection was a major criteria for eligibility, although there was no central review for pathology. Chemotherapy began from 2 to 8 weeks after surgery, for 6 months. The size of the study population was calculated to detect an improvement in DFS at 4 months (endpoint). The characteristics of both arms were well balanced in terms of clinical characteristics, tumor status and surgical procedures. Both DFS [11.4 months in the gemcitabine plus erlotinib arm *vs.* 11.4 months in the control arm (HR 0.94; 95% CI, 0.76–1.15, P=0.26] and OS were not different between the two arms or in the different subgroups according to stratification (24.5 *vs.* 26.2 months). Rash occurred in 77% of patients (Grade 1: 31%, Grade 2: 28%, Grade 3–4: 8%) in the experimental arm and its severity did not influence OS. This was discordant with two studies showing that patients with skin rash had a better tumor control (12,13). Dose escalation of erlotinib increased the rate of patients with rash and did not improve OS.

Fourteen percent of the patients in the Sinn study had postoperative serum CA 19.9 levels >100 kU/L in both arms and they had a significantly reduced median DFS and OS compared to those with values below this level. Similarly, 17% of patients in the ESPAC-4 trial had a postoperative serum level >92 kU/L with a median survival of 13.1 (10.8–16.2) months *vs.* a median survival of 29.6 (26.6–32.1) months in patients with lower values. In the Sinn study, full adjuvant treatment (six cycles) was completed in 145 patients (66%) in the combination arm and 160 patients (74%) in the gemcitabine arm.

Treatment started more than 7 weeks after surgery in 139 patients (66%) in the combination arm and only 105 patients (49%) in the gemcitabine arm. A delay of more than 6 weeks was associated with a worse DFS (10.9 *vs.* 12.2 months, P=0.026), but did not influence OS, possibly due to insufficient power in the study. The authors suggest that the longer delay in the combination arm was probably due to a desire to limit adverse effects. In view of ESPAC3 results, Valle *et al.* (14) suggested that the delay to the start of adjuvant chemotherapy did not influence OS (HR 0.985; 95% CI, 0.956–1.015), but OS was increased in patients who completed the full treatment compared to those who did not (HR 0.156; 95% CI, 0.443–0.601).

Sinn *et al.* (1) mention certain limitations to their study. First, this was an open label study and no placebo was given to the patients in the gemcitabine arm. Also, the lines of treatment after tumor progression were not standardized, thus two thirds of patients received an undefined chemotherapy, while a small percentage received radiation therapy (7%), and even second a surgical procedure (2%). It cannot be excluded that second line treatments following gemcitabine based-chemotherapy (i.e., FOLFIRINOX combination) could influence OS. Moreover, quality of life was not defined as a secondary end point. Finally, there was no central review of imaging even though defining tumor relapse can be difficult, particularly when it is locoregional.

The study by Sinn *et al.* (1) provides further evidence on the value of erlotinib in PDAC, as other negative studies in both metastatic or locally advanced forms of this cancer have been published (15,16).

The results of the PRODIGE 24 study comparing gemcitabine to the combination FOLFIRINOX in adjuvant setting were presented at the ASCO meeting 2018 (17). Four hundred and ninety-three patients were

randomized in two well balanced arms. Resection was R1 in 40.1%/45.7% of cases in FOLFIRINOX and gemcitabine arms, respectively. Despite the rate of relative dose-intensity >70% was more reduced in the FOLFIRINOX arm than the gemcitabine one (48.7% and 91.4%, respectively), the DFS, main objective of the study, was clearly higher with FOLFIRINOX [21.6 months (95% CI, 17.7–27.6)] *vs.* than with gemcitabine [12.8 months (95% CI, 11.7–15.2)]; in addition, OS was better in the FOLFIRINOX arm [54.4 (95% CI, 41.8–not reached) months] than in the gemcitabine arm [35.0 (95% CI, 28.7–43.9) months]. This combination will be a new standard of care in the adjuvant setting, at least in Western countries. Finally, the results of the APACT study (NCT01964430) comparing gemcitabine plus nab-paclitaxel *vs.* gemcitabine are pending.

In conclusion, the combination of erlotinib and gemcitabine did not improve survival in patients who underwent R0 surgical resection for PDAC in the study by Sinn *et al.* (1). Twelve years after the publication by Moore *et al.* (12) erlotinib seems to have a very limited impact on the management of this cancer, whatever the stage of development.

Acknowledgements

Thanks to Mrs. Dale Roche-Lebrec for her help in the edition of this manuscript.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Sinn M, Bahra M, Liersch T, et al. CONKO-005: Adjuvant Chemotherapy With Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. J Clin Oncol 2017;35:3330-7.
2. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med 2014;371:2140-1.
3. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001;358:1576-85.
4. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200-10.
5. Oettle H, Neuhaus P, Hochhaus A, 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.
6. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 2010;304:1073-81.
7. Greenhalf W, Ghaneh P, Neoptolemos JP, et al. Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 trial. J Natl Cancer Inst 2014;106:djt347.
8. Svrcek M, Cros J, Maréchal R, et al. Human equilibrative nucleoside transporter 1 testing in pancreatic ductal adenocarcinoma: a comparison between murine and rabbit antibodies. Histopathology 2015;66:457-62.
9. Neoptolemos JP, Palmer DH, Ghaneh P, et al. 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.
10. Uesaka K, Boku N, Fukutomi A, 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.
11. Sinn M, Liersch T, Gellert K, et al. CONKO-006: A randomized double-blinded phase IIb-study of additive therapy with Gemcitabine plus Sorafenib/Placebo for patients with R1-resection of pancreatic cancer. Onkologie 2011;34:59-59.
12. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-6.
13. Van Cutsem E, Li CP, Nowara E, et al. Dose escalation to rash for erlotinib plus gemcitabine for metastatic pancreatic cancer: the phase II RACHEL study. Br J Cancer 2014;111:2067-75.
14. Valle JW, Palmer D, Jackson R, et al. Optimal Duration and Timing of Adjuvant Chemotherapy After Definitive Surgery for Ductal Adenocarcinoma of the Pancreas: Ongoing Lessons From the ESPAC-3 Study. J Clin Oncol 2014;32:504-12.
15. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and

erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 2009;27:2231-7.
16. Hammel P, Huguet F, van Laethem JL, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. JAMA 2016;315:1844-53.
17. Conroy T, Hammel P, Hebbar M, et al. Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas. J Clin Oncol 2018;36:abstr LBA4001.

Cite this article as: Wisniewksi M, Placide PA, Granier S, Al Shatti Y, Al Qalaf S, Bouattour M, Lamuraglia M, Hammel P. Adjuvant chemotherapy with gemcitabine plus erlotinib versus gemcitabine alone for patients with resected pancreatic ductal adenocarcinoma: is there a role for erlotinib? Review of the open label phase III trial CONKO 005. HepatoBiliary Surg Nutr 2018;7(5):399-402. doi: 10.21037/hbsn.2018.08.03

