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Editorial

Induction chemotherapy in borderline (non-)resectable pancreatic cancer: a unique window of opportunity for understanding pancreatic cancer



The management of pancreatic cancer needs strong adaptation and improvement in care and research if we want to successfully increase its very bad outcome.

The clinical landscape of pancreatic cancer is currently divided into four subentities: resectable, borderline resectable, locally advanced and metastatic disease. There are schematically two main backbone regimens, i.e. FOLFIRINOX and Nab-PACLITAXEL-GEMCITABINE (NP-G), both of which are closely active in the metastatic setting [1,2]. The FOLFIRINOX regimen is now proven as a new standard in the adjuvant setting in fit patients after surgery and is more and more used as neoadjuvant/induction therapy of borderline or locally advanced tumours, although there is not yet a high level of evidence in this emerging setting [3,4]. Thereby, there is clearly a place in this setting for developing new therapeutic combinations and strategies based on these backbone regimens that may allow surgeons to increasingly attempt for R0 resection after tumoural downshrinking/downstaging.

In the current issue of *EJC* [5], Reni *et al.* reported a randomised phase II study, exploring the activity of two alternative regimens to FOLFIRINOX in borderline resectable and locally advanced disease, based on NP-G (nab-paclitaxel -gemcitabine) in one arm and NP-G, strengthened by platinum and capecitabine (PNPXG). PNPXG regimen was previously evaluated in phase I and was thereafter evaluated in induction/neoadjuvant setting. The conclusions of their study showed that this multichemotherapy regimen was feasible, promisingly active in terms of disease response and control, resectability rate and pathological response and could be investigated in a phase III trial.

This report has undoubtedly valuable merits, despite some weakness and limitation. The first strong point is its completion, after successful randomisation of 54 patients in a difficult setting, well conducted and providing completed data. The second one is the accurate eligibility, definition and selection of patients based on clear vascular involvement and (non-)resectability criteria, which were reviewed by a multidisciplinary expert board before inclusion and randomisation. This is unequivocally the major requirement for driving a well-conducted study in this highly heterogeneous setting where the concept of borderline vs definitely unresectable disease may evolve overtime, thanks to more active therapeutic regimens [6]. The third one is the good choice of the primary end-point, i.e. R0 resectability rate, and the secondary ones, which remarkably include pathological response besides outcome parameters. On the other hand, this study displays some weaknesses. The choice of the experimental regimen, although constituting a possible alternative to FOLFIRINOX, remains questionable regarding its future use, even as experimental. Its relative activity/toxicity balance, although promising, needs to be further evaluated or randomly compared with this of folfirinnox. In the present study, purely explorative, the apparently better activity of PNPXG on NP-G in terms of clinical (CA 19.9 and Response Evaluation Criteria in Solid Tumours) and pathological response and progression-free survival should be interpreted with caution because both arms were imbalanced (by 'chance') regarding the borderline/locally advanced status at the baseline (better theoretical prognosis in the NP-G group) but receiving quite differently additional chemoradiation after the initial chemotherapy (88% for the PNPXG group vs 57% for the NP-G group). The question of adding

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Table 1 The clinical landscape of non-metastatic pancreatic cancer.

Entity	Resectable	Borderline resectable	Locally advanced
Incidence	15–20%	7–10%	15–20%
Survival (optimal)	35 → 54 months	Depend on resectability (up to 24–30 months if R0)	13 → 24 months (highly heterogeneous series)
Standard management	Surgery → adjuvant therapy	Upfront attempt to surgery vs induction/neoadjuvant therapy → surgery	Induction chemotherapy then reevaluation No chemoradiation as Standard of care
Level of evidence/ recommendation	I/A	IV/B	I/A
Chemotherapy used	FOLFIRINOX in fit patients Gemcitabine-capecitabine or gemcitabine alone if contraindications to FOLFIRINOX	FOLFIRINOX NP-G	Gemcitabine-based FOLFIRINOX
Experimental design/ End-point	Preoperative/perioperative vs postoperative chemotherapy	Optimal sequence combining chemotherapy-chemoRT or SBRT R Phase II/ R0 rate-pCR translational	Folfirinox vs NP-G Maintenance therapy? New drugs
	Phase III/ DFS/OS		R phase II PFS/OS

RT, radiation therapy; NP-G, nab-paclitaxel-gemcitabine; SBRT, stereotactic body radiation therapy; pCR, pathological Complete Response; PFS, progression-free survival; OS, overall survival.

(chemo)radiation in such trials is still not resolved and highlights the difficulty to conduct a pure trial in this population of patients in whom resectability definition is difficult to be standardised and evaluated overtime after chemotherapy induction. Clearly, chemoradiation therapy may influence the course of the disease when administered before surgery and seems to induce more intense pathological response and changes than chemotherapy alone [7]. Unfortunately, we are lacking on randomised comparison of chemo vs chemoradiation and one French trial is currently recruiting patients in a randomised phase II trial where chemoradiation is randomly allocated after six cycles of folfirinox (PANDAS-PRODIGE trial; NCT02676349).

In summary, rather than drawing some conclusions on the activity profile of the proposed regimen (PNPXG), this well-conducted trial should prompt us to promote additional trials in well-defined populations. It becomes mandatory to clearly differentiate truly resectable, borderline resectable and locally advanced disease with no chance to reverse the situation in our future trials. For truly resectable disease, neoadjuvant (or perioperative) folfirinox should be compared with strict adjuvant folfirinox which is now the standard of care for fit patients, and improving outcomes should be the main end-point. Borderline disease offers a unique window to evaluate new strategies and new combinations, based on the existing backbone active chemotherapies, but reinforced by new promising agents and radiation therapy administered as stereotactic body radiation therapy which is known as immunogenic and possibly completed by

testing immunomodulation of this sequence. This should be conducted in small randomised phase II trials or in proof-of-concept studies with in-depth evaluation and monitoring of tumoural changes, performed by dynamic imaging, liquid biopsies and pathological and molecular assessment on the resected specimens. Primary end-point of such trial should be pathological response, probably better than the resection rate.

Locally advanced disease also deserves specific exploration with new combinations but should be clearly separated from borderline disease as it will never succeed to be resected and will harbour consequently different and variable prognosis as previously reported in meta-analysis [4]. The disease control rate could be chosen as the end-point, including maintenance therapy. The standard and experimental approach in the clinical landscape of non-metastatic pancreatic cancer is summarised in Table 1.

In the era of a better comprehensiveness of the molecular and taxonomic profile of pancreatic cancer subdivided in different genomic groups [8], it is mandatory to increase the quality of our trials by improving our patients' selection, our imaging evaluation at the baseline and on therapeutic course and our surgical and pathological procedures and by incorporating translational research allowing to predict treatment benefit. The study from Reni *et al.* opens the way to do so.

Conflict of interest statement

None declared.

References

- [1] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; 364:1817–25.
- [2] Von Hoff DD, Goldstein D, Renschler MF. Albumin-bound paclitaxel plus gemcitabine in pancreatic cancer. *N Engl J Med* 2014;370:479–80.
- [3] Conroy Th, 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. suppl; abstr LBA4001.
- [4] Suker M, Beumer B, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol* 2016;17:801–10.
- [5] Reni M, Zanon S, Balzano G, et al. A randomized phase 2 trial of nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in locally advanced or borderline resectable pancreatic adenocarcinoma. *Eur J Cancer* 2018;102:95–102.
- [6] Gilbert JW, Wolpin B, Clancy T, et al. Borderline resectable pancreatic cancer: conceptual evolution and current approach to image based classification. *Ann Oncol* 2017;28:2067–76.
- [7] Pietrasz D, Marthey L, Wagner M, et al. Pathologic major response after FOLFIRINOX in prognostic for patients secondary resected for borderline or locally advanced pancreatic adenocarcinoma: AGEO-French, prospective, multicentric cohort. *Ann Surg Oncol* 2015;22:S1196–205.
- [8] Puleo F, Nicolle R, Blum Y, et al. Stratification of pancreatic ductal adenocarcinomas based on tumor and microenvironment features. *Gastroenterology* 2018;5085(18):34919-9.

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