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Commentary

Clinical Trials in Pancreatic Cancer: A Long Slog

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Disclosures of potential conflicts of interest may be found at the end of this article.

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most difficult-to-treat cancers, with a 5-year survival rate of only 8%, one of the lowest of all cancers. Even if the cancer is resected in a curative way and the patient is treated with intense adjuvant chemotherapy for 6 months, most patients relapse and die of disease; median survival in the recent ESPAC-4 trial was 28 months [1]. Almost half of patients present with metastatic disease and face a median overall survival of less than 12 months [2].

The development of effective systemic therapy has lagged behind that of other tumor types. Much effort was required to identify chemotherapy regimens that could significantly improve survival over gemcitabine alone. A major step forward was the identification of the combination chemotherapy regimen FOLFIRINOX, which improved survival (11.1 months versus 6.8 months over gemcitabine alone in the PRODIGE study [3]). A second study, the MPACT trial, identified the addition of nab-paclitaxel to gemcitabine as effective, with an 8.5-month overall survival for the combination versus. 6.7 months for gemcitabine alone [4]. Although FOLFIRINOX appears to have greater benefit, it is a more intense regimen, and a number of modified regimens are being adopted, although without clear data supporting equivalence with the original regimen [5–9]. Given that the patient population on the MPACT trial was older and was weighted toward poorer performance status, some investigators consider the two regimens, FOLFIRINOX and gemcitabine plus nab-paclitaxel, to be more similar than different [10]. A small study from Japan comparing the two regimens found a median progression-free survival of 3.7 months for FOLFIRINOX versus 6.5 months for gemcitabine plus nab-paclitaxel [11]. Similarly, in a retrospective analysis, modified FOLFIRINOX (dose-reduced irinotecan and 5-FU bolus omitted) compared with gemcitabine/nab-paclitaxel showed a median progression-free survival of 5.7 versus 6.5 months and a median overall survival of 11.5 versus 14 months, respectively [12].

Considering the two regimens likely comparable, many investigators have turned their efforts toward improving the gemcitabine/nab-paclitaxel combination by the addition of a third agent. The fact that gemcitabine/nab-paclitaxel is well-tolerated, even in the elderly [13], offers an attractive platform on which to make such an addition. The study by Ko et al. takes this approach [14], along with almost 30 other trials recruiting patients, according to ClinicalTrials.gov.

Numerous trials were performed attempting to improve over gemcitabine monotherapy—summarizing several meta-analyses, almost 14,000 patients across 47 trials were invested in this effort [2, 15–19]. Whether it will require 14,000 patients to make another incremental step over gemcitabine/nab-paclitaxel remains to be determined.

Also in this issue, O'Reilly et al. report another trial using gemcitabine/nab-paclitaxel as a platform [20]. Necuparanib, a heparan sulfate considered to have antitumor and antimetastatic activity, was studied in combination with gemcitabine/nab-paclitaxel in a phase I study in 39 patients, with a partial response rate of 38% and a median survival of 15.6 months in those who received at least one cycle. These results supported continuation of the study into a randomized phase II design that was discontinued at an interim analysis, as the three-drug combination did not achieve a sufficient level of activity to warrant trial continuation.

In the randomized double-blinded phase II trial, Ko et al. evaluated the efficacy of gemcitabine/nab-paclitaxel plus either apatorsen, an antisense oligonucleotide targeting mRNA of the heat shock protein 27 (Hsp27), or placebo in patients with previously untreated metastatic PDAC [14]. The rationale for this study was that Hsp27, a protein chaperone that promotes cell survival under stress conditions, is induced by chemotherapy, radiation, and oxidative stress [21]. In vitro data suggested that Hsp27 may play a key role in resistance to gemcitabine [22]. Apatorsen is an antisense oligonucleotide that binds to Hsp27 mRNA and blocks its translation [23]. In this trial, 132 patients with metastatic PDAC were enrolled, 66 in the apatorsen arm and 66 in the control arm. Median PFS and OS were disappointingly poor, 2.7 and 5.3 months, in the apatorsen arm versus 3.8 and 6.9 months in the gemcitabine/nab-paclitaxel only arm, respectively. The authors were not able to identify prognostic factors that might explain the poorer overall survival at 6.9 months for the gemcitabine/nab-paclitaxel only arm, relative to the original MPACT data. It may be that increasing confidence in the use of gemcitabine/nab-paclitaxel has led to treatment of patients with worse performance status and disease characteristics than in the original trial.

On closer inspection of the trial, one does observe a trend in the poor prognostic subgroup with high serum levels of Hsp27 toward longer PFS and OS with apatorsen, 3.3 and 3.3 months versus 0.9 and 1.0 months in the gemcitabine/nab-

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paclitaxel only arm. Although the number of subjects was too small to draw any conclusions, the findings seem to indicate that this subgroup could benefit from inhibition of Hsp27, suggesting that the question deserves a second look.

One proposed hypothesis for chemotherapy failure in PDAC is the formation of a dense stroma around the tumor cells that blocks drug access to the tumor. A nanoliposomal formulation of irinotecan aims to overcome the stromal barrier and improve drug delivery to the tumor. The NAPOLI-1 trial showed that the combination of nanoliposomal irinotecan with 5-FU/leucovorin improved OS over either of these therapies alone in patients previously treated with gemcitabine/nab-paclitaxel [24]. An alternate approach to overcoming the dense stroma is the use of PEGylated recombinant hyaluronidase (PEGPH20), which reduces the accumulation of hyaluronic acid (HA) in the tumor stroma. A randomized phase II trial showed that the addition of PEGPH20 to gemcitabine plus nab-paclitaxel led to a 46% overall response rate, compared with 34% with the two chemotherapy drugs alone in patients with HA-high PDAC [25]. A confirmatory randomized phase III trial is ongoing.

Systemic genomic sequencing has revealed that PDAC is not typically a heavily mutated tumor [26]. The most consistently mutated genes are *KRAS, CDKN2A, TP53,* and *SMAD4/DPC4* [27]. Mutational signatures have also been cataloged—relating profiles of actual nucleotide variants to cancer-causing processes—identifying 4 signatures: age-related, double-strand break repair (DSBR)-deficient, mismatch repair (MMR)-deficient, and an ill-defined group [28]. DSBR-deficient (11% of cases) and MMR-deficient (2% of cases) signatures were associated with evidence of increased immunogenicity. These signatures could eventually aid identification of agents to add to the nab-paclitaxel/gemcitabine platform, including immunotherapy strategies [26]. The fact that most tumors bore age-related and not immunogenic signatures speaks to the need to find altogether different approaches to therapy.

In summary, the presented study points to the importance of reporting "negative" clinical trials—so valuable for what can be learned. Indeed, this study can be viewed in the context of all the studies that attempted to improve over gemcitabine monotherapy. The lower overall survival in the treatment population in the study by Ko et al. points to the importance of continuing to run randomized trials in pancreatic cancer, which is demanded by the variable complexity and heterogeneous nature of the patient population. It also points to the important role of the oncology community in supporting these trials through referral of patients for clinical trials whenever possible. Numerous clinical trials are currently available for patients with PDAC, ranging from neoadjuvant to refractory metastatic disease, and we strongly encourage participation in such trials [29].

Disclosures

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Editor's Note:

See the related articles, "A Randomized, Double-Blinded, Phase II Trial of Gemcitabine and Nab-Paclitaxel Plus Apatorsen or Placebo in Patients with Metastatic Pancreatic Cancer: The RAINIER Trial," by Andrew H. Ko et al. on page 1427 and "Saftey, Pharmacokinetics, Pharmacodynamics, antitumor activity of necuparanib combined with nabpaclitaxel and gemcitabine in patients with metastatic pancreatic cancer: Phase I results" by Eileen M. O'Reilly et al., on page 1429.