VOLUME 32 · NUMBER 23 · AUGUST 10 2014

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

New Option for the Initial Management of Metastatic Pancreatic Cancer?

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In the October 31, 2013, issue of the *New England Journal of Medicine*, Von Hoff et al[1] published an important article describing the results of a randomized clinical trial conducted in patients with metastatic pancreatic cancer that compared gemcitabine with a combination of gemcitabine and nab-paclitaxel. In this trial, 861 patients were randomly assigned: 431 to gemcitabine plus nab-paclitaxel and 430 to gemcitabine alone. The high-level results demonstrated a median overall survival of 8.5 months in the nab-paclitaxel group compared with 6.7 months in the gemcitabine group. The hazard ratio for death was 0.72 (95% CI, 0.62 to 0.83; $P < .001$). Other end points, including progression-free survival and response rate, were superior with the combination. Grade ≥ 3 neutropenia occurred in 38% of the patients treated with gemcitabine plus nab-paclitaxel, with 3% of these instances resulting in febrile neutropenia. Twenty-six percent of the patients received growth factors. Cumulative peripheral neuropathy occurred in 17% of the patients treated with nab-paclitaxel, and it was managed with temporary discontinuation of nab-paclitaxel followed by a reduction in dose. Overall, however, 71% of the nab-paclitaxel doses were delivered at the intended starting dose.[1]

On the basis of these results, there are now two combination cytotoxic chemotherapy regimens with activity in patients with untreated metastatic pancreatic cancer: gemcitabine plus nab-paclitaxel and the combination of fluorouracil, irinotecan, and oxaliplatin known as FOLFIRINOX. The pivotal FOLFIRINOX trial (Partenariat de Recherche en Oncologie Digestive 4/Action Clinique Coordonnées en Cancérologie Digestive 11 [PRODIGE4/ACCORD 11]) also targeted patients with metastatic pancreatic cancer, randomly assigning 342 patients to receive FOLFIRINOX or gemcitabine. In that trial, the median overall survival was 11.2 months for patients treated with FOLFIRINOX and 6.8 months for patients treated with gemcitabine.[2] However, despite the encouraging efficacy of FOLFIRINOX, the challenge with this regimen is its toxicity, with 46% of the FOLFIRINOX-treated patients developing grade 3 or 4 neutropenia, 5% febrile neutropenia, and 42% requiring growth factor support with filgrastim. The incidence of grade 3 or 4 diarrhea and sensory neuropathy were also significantly higher in the FOLFIRINOX group.[2] However, despite the higher rates of adverse events with FOLFIRINOX relative to gemcitabine, FOLFIRINOX conferred a benefit by slowing deterioration in quality of life, presumably because of the anticancer activity of the regimen.

Recognizing the limitations of cross-trial comparisons, practicing oncologists are now faced with the question of which of these two regimens should be considered for the first-line management of patients with metastatic pancreatic cancer. Both regimens are clearly active. As described in the reports, there are differences in the patient populations being treated. For example, patients treated with gemcitabine plus nab-paclitaxel compared with patients treated with the FOLFIRINOX regimen tended to be somewhat older (10% of patients were age ≥ 75 years), had a slightly worse performance status (7% to 8% of patients had Karnofsky performance status $\leq 70\%$), fewer patients had peritoneal metastases, and greater numbers of patients had increases in CA19-9 ≥ 59 times the upper limit of normal. Similar numbers of patients had biliary stents placed for management of obstructive jaundice. Patients with a borderline Karnofsky performance status and higher baseline CA19-9 would generally be considered to have a higher tumor burden and poorer prognosis, but fewer patients with peritoneal involvement would be considered favorable. Nevertheless, how these differences in patient populations treated in the two trials impacted outcome is difficult to judge. This perspective is strongly supported by the fact that the median survival of the gemcitabine control arm of both studies was essentially identical. Recognizing the difficulty inherent in comparing a regimen that uses a novel agent (nab-paclitaxel) with a combination of well-established cytotoxic agents (fluorouracil, oxaliplatin, and irinotecan), a prospective trial conducted through the newly constituted National Cancer Institute National Clinical Trials Network may provide the perfect vehicle for addressing such a question.

The statistical design of the Von Hoff trial[1] is perhaps superior in that the trial was larger and prospectively designed with overall survival as its primary end point (although the power of the trial was increased from 80% to 90% after accrual was initiated) whereas the FOLFIRINOX phase III trial was initially sized to detect a 15% improvement in 6-month survival and was subsequently amended to detect a 3-month (from 7 to 10 months) improvement in median overall survival with FOLFIRINOX compared with single-agent gemcitabine. The FOLFIRINOX trial also began with a randomized phase II component that demonstrated substantial anticancer activity with the multiagent regimen, but the larger size of the Von Hoff trial[1] improved our confidence in the median event statistics, including the median survival and median progression-free survival results. Ultimately, judging between trial results by assessing overlap in CIs on individual statistics such as median OS is perilous, and the only objective way to resolve this uncertainty will be to mount a well-designed phase III trial.

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A more pragmatic perspective on the relevance of the superiority question might be that in the absence of a firmly established second-line regimen, for patients opting out of participation in a clinical trial it is quite likely that patients with good performance status progressing on FOLFIRINOX could be treated with gemcitabine plus nab-paclitaxel and vice versa. Prospective data demonstrating that additional chemotherapy can be administered to patients experiencing worsening disease on FOLFIRINOX is limited, but in the FOLFIRINOX trial, close to 50% of the patients were treated with gemcitabine or a gemcitabine-containing regimen after experiencing disease progression on FOLFIRINOX.[2] Nonetheless, a prospective phase III trial clearly could be designed to address the optimal first-line regimen as assessed by survival and quality of life as well as to determine the feasibility and impact of second-line therapy, questions raised by the results generated by these two trials. The large numbers of patients diagnosed with pancreatic cancer also make it possible to conduct a large phase III trial and, in parallel, study novel interventions in smaller pilot and phase II trials designed to test concepts that may identify strategies with a more dramatic impact on survival. The question of whether to prioritize the resources to conduct a large phase III trial designed to establish the superiority of first-line management of patients with metastatic pancreatic cancer with FOLFIRINOX or gemcitabine plus nab-paclitaxel is a difficult one. Different investigators may judge the best allocation of resources differently, but in our view, it is not as important to commit substantial patient resources to formally answer the superiority question through a prospective randomized trial in a situation in which many patients will be treated with both regimens over the course of their disease management.

On the basis of these considerations, the comparable activity and manageable reported toxicity profile of the gemcitabine plus nab-paclitaxel combination suggests that this is a reasonable initial treatment alternative to FOLFIRINOX. The toxicity and possible survival advantage for FOLFIRINOX relative to gemcitabine plus nab-paclitaxel suggest that this may be the best initial approach for younger patients with well-preserved performance status. Gemcitabine plus nab-paclitaxel may be a better starting option for older, more symptomatic patients.

With these results in hand, what should be the approach to the next generation of trials for pancreatic cancer? Although several strategies could be considered, what should be de-emphasized are trials in which all patients with metastatic pancreatic cancer are considered to be equally likely to respond to a single intervention. The best available models of pancreatic cancer coupled with pilot clinical trials in patients with refractory pancreatic cancer should be used to provide a more detailed understanding of the intervention and to identify subsets of pancreatic cancer likely to benefit from a given investigational approach.[3,4] Without this, most interventions are in essence empirical trials of a novel approach in an extremely heterogeneous cancer. Historically, the empirical clinical testing of novel agents has been at the expense of many negative phase III trials, with most patients treated in the context of these studies not deriving any sustained benefit from therapy.

From our perspective, the more rational approach would be to continue to dissect the molecular genetics and molecular biology of patients with pancreatic cancer. The goal of this approach would be to identify subsets of pancreatic cancers that, through their constellation of genetic and molecular alterations, would be expected to respond to single agents or combinations of targeted agents, perhaps even in combination with a cytotoxic backbone. The biggest challenges to this approach include the almost ubiquitous mutation in the difficult-to-target *KRAS* oncogene and the fact that other high-frequency genetic events occurring during pancreatic carcinogenesis involve the loss of tumor suppressors such as *TP53* or *CDKN2A*.[5] Continuing efforts to genetically stratify patients with pancreatic cancer should be coordinated with the renewed emphasis on developing strategies to directly inhibit *KRAS* that may be showing early promise and the efforts targeting *KRAS* that are currently beginning at the National Cancer Institute under the leadership of Dr Frank McCormick.[6] Additional strategies include ongoing efforts using synthetic lethal screens to identify molecular targets that render cells vulnerable to cell death in the presence of mutations in *KRAS* or identification of targets that result from enhanced cellular signaling through *KRAS*-mediated pathways.[7,8]

A second strategy would be to formally explore the potential of immunologic approaches such as CD40 agonists and T-cell engineering strategies.[9,10] Such strategies fit nicely with the current emphasis on understanding the unique role of the local host response to pancreatic cancer, and preclinical studies suggesting that the prolific stroma associated with pancreatic cancer serve as a barrier to the distribution of cytotoxic chemotherapy into the pancreatic primary tumor.[3,11,12] The extent to which a stromal barrier function can be targeted in metastatic pancreatic cancer is currently being addressed in trials using stromal disrupting agents in combination with chemotherapy. Finally, studies of the cellular metabolic consequences of mutated *KRAS* and adaptation of pancreatic cancer cells to a nutrient-depleted local environment suggest that specific metabolic pathways that are altered during pancreatic carcinogenesis can be targeted by agents designed to inhibit aerobic glycolysis, glutamine metabolism, or other metabolic pathways that are altered during cellular transformation and cancer progression.[13-16]

To summarize, the trial reported by Von Hoff et al[1] clearly adds to the treatment options available to patients with metastatic pancreatic cancer, and its toxicity profile should allow this regimen to be effectively integrated into the multimodality management of patients with potentially resectable, borderline resectable, and locally advanced pancreatic cancer. However, it is also clear that the limited advances achieved with this cytotoxic chemotherapy regimen should not impede our long-term efforts to develop more specific and effective systemic therapies for patients affected by this difficult disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Von Hoff DD, Ervin T, Arena FP, et al: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369:1691-1703, 2013

2. Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-1825, 2011

3. Olive KP, Jacobetz MA, Davidson CJ, et al: Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science 324:1457-1461, 2009

4. Kim MP, Evans DB, Wang H, et al: Generation of orthotopic and heterotopic human pancreatic cancer xenografts in immunodeficient mice. Nat Protoc 4:1670-1680, 2009

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5. Jones S, Zhang X, Parsons DW, et al: Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science 321:1801-1806, 2008

6. Ostrem JM, Peters U, Sos ML, et al: K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature 503:548-551, 2013

7. Gysin S, Salt M, Young A, et al: Therapeutic strategies for targeting ras proteins. Genes Cancer 2:359-372, 2011

8. Luo J, Emanuele MJ, Li D, et al: A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the Ras oncogene. Cell 137:835-848, 2009

9. Beatty GL, Torigian DA, Chiorean EG, et al: A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. Clin Cancer Res 19:6286-6295, 2013

10. Barrett DM, Singh N, Porter DL, et al: Chimeric antigen receptor therapy for cancer. Annu Rev Med 65:333-347, 2014

11. Thompson CB, Shepard HM, O'Connor PM, et al: Enzymatic depletion of tumor hyaluronan induces antitumor responses in preclinical animal models. Mol Cancer Ther 9:3052-3064, 2010

12. Provenzano PP, Cuevas C, Chang AE, et al: Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 21:418-429, 2012

13. Lyssiotis CA, Cantly LC: Targeting metabolic scavenging in pancreatic cancer. Clin Cancer Res 20:6-8, 2014

14. Chini CC, Gonzalez-Guerrico A, Nin V, et al: Targeting of NAD metabolism in pancreatic cancer cells: Potential novel therapy for pancreatic tumors. Clin Cancer Res 20:120-130, 2014

15. Son J, Lyssiotis CA, Ying H, et al: Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. Nature 496:101-105, 2013

16. Ying H, Kimmelman AC, Lyssiotis CA, et al: Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell 149:656-670, 2012

DOI: 10.1200/JCO.2013.54.4155; published online ahead of print at www.jco.org on June 30, 2014

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