Pancreatic Cancer: Steps in the Right Direction

One of the most feared among cancer diagnoses, pancreatic ductal adenocarcinoma (PDA) has historically represented the worst of all worlds. Features include the following: a cancer with an insidious biology; diagnosis at an advanced stage in a previously asymptomatic patient; technically difficult surgery due to location often rendering small-volume disease inoperable; and drug-resistant disease making chemotherapy of little use. Progress has been hard to come by and has focused on chemotherapy options, given the advanced presentation of PDA or invariable recurrence after surgery. The first successful chemotherapy—with success defined as gaining regulatory approval for a PDA indication—was gemcitabine, approved in 1996 on the basis of its ability to improve survival and to provide "clinical benefit." The latter was a novel descriptor including weight gain and pain reduction, important considerations given that gemcitabine improved survival by only 1.5 months. While a recent randomized trial reported that FOLFIRINOX compared with gemcitabine improved median overall survival by 4 months, everyone agrees we still have a long way to go.

This CCR Focus series addresses progress in our understanding of the biology of the disease, identifying potential therapeutic targets. With an average of 63 genetic abnormalities per tumor, it seems unlikely that individual mutations will be individually targeted as in ALK-rearranged or EGFR-mutant lung cancer. However, as highlighted in the overview by Guest Editors Manuel Hidalgo and Daniel D. Von Hoff, there are multiple avenues to be explored. In addition to the search for a mutation that could be successfully targeted, experts point to the critical role of tumor stroma in determining drug resistance; the intratumoral heterogeneity of PDA cell types, including a subset with stem cell properties; and the altered metabolic pathways. Together these represent multiple approaches for discovery and clinical trial development.

While progress is being made on many fronts in better understanding PDA, as evidenced from the articles in this CCR Focus section, one area that needs enhanced development is better strategies for early detection. Considering how very refractory PDA has been and is likely to remain once diagnosed, and given the evidence that the disease develops gradually over as many as 15 years, one could envision a strategy aimed at earlier detection when the disease could be more amenable to surgical resection. Admittedly, such a strategy is not risk free and would suffer from the problems all early detection strategies must contend with. But given the progress in genomic characterization of early lesions discussed in this CCR Focus section and the very large problem presented by PDA when detected in the clinic, early detection might be another way forward.

As with every edition of CCR Focus, it is our hope that the articles will inform and intrigue both the expert in the field and the interested but nonexpert observer.

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