Viewpoint

Does neoadjuvant therapy improve survival in pancreatic adenocarcinoma?

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Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with early recurrence. Currently, the 5-year survival of pancreatic cancer is 10%, with less than 40% survival even in localized disease (1). The early distant recurrence rate, following surgical resection, is likely driven by the presence of occult micro-metastasis at diagnosis, warranting the use of systemic therapy.

Systemic therapy in PDAC has been extensively studied in the adjuvant setting and to a lesser extent in the neoadjuvant setting. Adjuvant chemotherapy has a definite survival benefit and is a cornerstone of the standard treatment protocol for pancreatic cancer (2). However, access to adjuvant therapy can be hindered by the morbidity associated with pancreatic surgery ultimately leading to poor prognosis. Neoadjuvant therapy (NAT) represents a valuable strategy to ensure patients access to systemic therapy and it is increasingly being utilized in patients with borderline resectable and locally advanced pancreatic adenocarcinoma. NAT impacts various prognostic markers of PDAC, including tumor size, lymph node (LN) positivity, CA19-9 levels, and newer biomarkers such as circulating tumor DNA (ct-DNA) (3). Complete response to NAT, albeit a rare occurrence, has been associated with improved survival in patients with PDAC. However, a definite survival benefit of NAT in PDAC remains to be demonstrated. While various retrospective studies have shown its merits in cohorts of borderline resectable and locally advanced disease, this remains to be seen in the setting of resectable disease. Furthermore, what constitutes the optimal preoperative regimen remains uncertain. The results from a recent randomized, multicenter, phase II trial of perioperative chemotherapy (12 weeks preoperatively–12 weeks postoperatively) in patients with resectable PDAC (SWOG S1505) suggested equivalent median overall survival (OS) between the two modern multidrug regimens FOLFIRINOX and gemcitabine nab-paclitaxel (23.2 *vs.* 23.6 months, respectively) (4).

The study authored by Kizy *et al.*, which preceded the results of the SWOGS1505, was designed to evaluate the merits of single agent gemcitabine compared to modern multidrug regimens (i.e., FOLFIRINOX and gemcitabine nab-paclitaxel) in a cohort of 36 patients with resectable PDAC. On an intention-to-treat analysis, the authors reported a statistically similar OS in patients treated with single agent gemcitabine (n=19) compared to multidrug regimens [FOLFIRINOX (n=11) and gemcitabine nab-paclitaxel (n=8)] thus suggesting no survival benefit with multidrug regimens (median survival 31.3 *vs.* 29.7 months, respectively).

NAT for PDAC has evolved over decades from gemcitabine monotherapy to combination chemotherapy. Gemcitabine was the drug of choice for pancreatic adenocarcinoma chemotherapy after its established survival benefit in the 1990s. However, clinical trials designed to compare the use of multi-agent therapy such as FOLFIRINOX and gemcitabine nab-paclitaxel, in the adjuvant setting, have established a definite survival benefit of both these latter chemotherapy regimens over single agent gemcitabine. As such, the remarkable results reported by Kizy *et al.* with using single agent gemcitabine in the neoadjuvant setting should be interpreted with caution

as the lack of comparative group undergoing a surgery first approach and the lack of information regarding receipt and type of adjuvant therapy following resection limit interpretation. Nonetheless, the study done by Kizy *et al*. (5) is one of the few retrospective studies that analyzed the survival benefit of NAT using an intent to treat analysis, including patients who failed chemotherapy and could not receive resection. Interestingly, and within the limitation of this small cohort, a greater portion of patients in the gemcitabine arm developed distant metastasis during NAT; similarly, fewer patients in the gemcitabine arm reached surgical resection (59% *vs*. 79%), although this difference was not statistically significant. Single agent gemcitabine, in the current era, is mostly used as a radiosensitizer in conjunction with radiation and is not the recommended choice for neoadjuvant chemotherapy, unless patients are unable to tolerate multidrug regimens. Various studies conducted during the last decade have associated improved progression free survival with FOLFIRINOX, and others have shown the possibility of improved survival, when used in the neoadjuvant setting. This, however, remains unestablished due to the higher use of 5-flurouracil based therapy in younger population with fewer comorbidities and better performance status. While phase II trials have shown no survival difference between patients treated with gemcitabine based and 5-FU based NAT (6), the literature still lacks phase III trials comparing these regimens in the neoadjuvant setting. Randomized control trials are currently underway to analyze these differences.

Ongoing research efforts hypothesize and suggest that pancreatic adenocarcinoma may have different cell lines, each of which may show variable sensitivity to 5-flurouracil based or gemcitabine-based chemotherapy (7). Additionally, mounting data suggest that new biomarkers may aid in differentiating cell lines that respond to various chemotherapy regimens thus aiding the selection of the optimal regimen. Overall, the accumulated experience aliments the concern that one size might not fit all, and neoadjuvant chemotherapy for pancreatic cancer may require an individualized approach.

Despite the lack of definitive evidence, NAT continues to gain a significant role in the systemic management of pancreatic adenocarcinoma even in seemingly resectable tumors. Further prospective randomized controlled trials examining the different chemotherapy regimens, their timing of administration and their impact on clinical outcomes are essential to tackle this highly morbid disease.

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Footnote

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