Editorial Commentary

Metastatic pancreatic cancer and opportunities for maintenance therapy

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Pancreatic cancer (PC) is the fourth deadliest malignancy in the United States with a 5-year survival rate of around 6% for patients with metastatic disease (1). In the United States, the median age of diagnosis of PC is 72 years, with 50–60% of patients metastatic at diagnosis (2,3). The older age of this patient population, absence of effective screening, and a high concordance of smoking, central obesity, and diabetes may contribute to the high incidence of metastatic disease at initial diagnosis and consequent poor overall survival (OS) (2). Patients typically present with vague but burdensome symptoms including fatigue, abdominal pain, nausea/vomiting, and emotional stress due to their prognosis.

The PRODIGE 4 trial established FOLFIRINOX as first-line therapy over gemcitabine with median OS of 11.1 *vs.* 6.8 months in the gemcitabine group (HR, 0.57; 95% CI, 0.45 to 0.73; P<0.001); PFS was also improved (6.4 *vs.* 3.3 months; HR, 0.47; 95% CI, 0.37 to 0.59; P<0.001) (1). While patients with preserved performance status (PS) may be candidates for the aggressive chemotherapy regimen of FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin), this regimen does carry a significant side effect profile that may detract from overall quality of life (QoL). The PRODIGE 4 trial demonstrated that FOLFIRINOX, compared to gemcitabine monotherapy, had higher incidences of neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy (1,4).

The PRODIGE 4 study does suggest, however, that reducing the tumor burden in PC may help preserve QoL. A secondary end-point of the PRODIGE 4 trial was to analyze health-related QoL for patients on each arm. Towards this end the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) version 3.0 was used to evaluate differences in global health status (GHS), physical functioning (PF), emotional functioning (EF), and role functioning (RF) at baseline and over time; a measure looking at time until definitive deterioration (TUDD) between the two treatment groups was also assessed (1,4). The survey that was provided to patients asked questions regarding five functions (physical, role, cognitive, emotional, and social), and nine symptoms (fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties). Despite the increased incidence of neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy with the FOLFIRINOX arm, there was ultimately no difference in EORTC QLQ-30 domains over time except for increased diarrhea in FOLFIRINOX (4). TUDD with respect to GHS was significantly longer in the FOLFIRINOX arm, which confirms a clinically meaningful improvement in QoL compared to gemcitabine despite being a more toxic regimen (4). This can perhaps be explained by the superiority of FOLFIRINOX compared to gemcitabine in treating the tumor burden of PC.

While FOLFIRINOX appears to prolong life and promote QoL in metastatic pancreatic cancer (mPC) patients, its usefulness is limited to the subset of patients whose baseline PS allows for such treatment. Many patients with PC present with poor performance (ECOG 2-3) and

are not candidates for FOLFIRINOX. Even among ECOG 1 patients, the survival advantage of FOLFIRINOX was seen predominantly in those who gave favorable responses to a question on sedentary lifestyle (4). Patients who were more sedentary and who were treated with FOLFIRINOX gained an average of two months of life as compared to the gemcitabine cohort, while those who were more active gained an average of six months with FOLFIRINOX as compared to gemcitabine alone. The prevalence of debilitating symptoms at presentation and the toxicity of first-line therapy underscores the need for targeted therapy and/or alternative regimens to improve longevity and QoL in these patients.

PARP inhibition may meet this need for a subset of patients. Germline mutations account for 5–10% of PCs, with *BRCA1/BRCA2* being found in 4–7% of patients with PC (2). *BRCA1/BRCA2* are DNA-damage response genes that identify double-stranded DNA-breaks and encode for proteins involved in homologous recombination repair (5). The development of olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, represents one of the latest novel agents that have undergone investigation for novel PC targeted therapy. Olaparib functions by inhibiting PARP proteins from identifying the double-stranded DNA breaks that the loss-of-function *BRCA1/BRCA2* are responsible for and the subsequent coordination of other DNA-damage response pathways; the result is an accumulation of genomic instability and ultimately cell death in the malignant cells (6). Olaparib was investigated in the POLO trial of BRCA mutant patients demonstrating its efficacy by improving median progression free survival (PFS) compared to placebo [7.4 *vs.* 3.8 months; hazard ratio (HR) for disease progression or death, 0.53; 95% confidence interval (CI), 0.35 to 0.82; P=0.004] (5). This represents an important step forward, yet these patients will still ultimately succumb to their disease and focus on QoL remains imperative. Understanding impact on QoL in patients on first-line therapy FOLFIRINOX and maintenance olaparib must be considered.

Similar to the PRODIGE 4 trial, a secondary endpoint of the POLO trial was to evaluate the efficacy of olaparib *vs.* placebo on health-related QoL (5). The EORTC QLQ-C30 was implemented again, also analyzing GHS, PF, RF, EF, social function (SF), cognitive function (CF), three multi-item symptom scales, five single-item symptom scales (pain, fatigue, nausea and vomiting, appetite loss and insomnia), and a single-item financial impact scale between the two arms of treatment (3,5). The domains were also analyzed with respect to time to sustained clinically meaningful deterioration (TSCMD) (5). Ultimately, there was no significant difference in GHS between olaparib and placebo (between-group difference –2.47; 95% CI, –7.27 to 2.33; P=0.31) (3). A non-significant improvement in TSCMD with respect to GHS was appreciated with olaparib (21.2 *vs.* 6.0 months; HR 0.72; 95% CI, 0.41–1.27; P=0.25) (3). A significantly decreased reduction in PF was seen in the olaparib arm –4.45 points (95% CI, –8.75 to –0.16; P=0.04) (3). Olaparib was responsible for significantly worse symptoms regarding fatigue, nausea/vomiting, and loss of appetite; however, only loss of appetite was deemed clinically significant (3). Essentially, patients enrolled in the POLO trial for maintenance therapy had excellent baseline GHS due to the efficacy of first-line FOLFIRINOX, having already appreciated an improvement in fatigue, nausea/vomiting, and pain (3). The POLO trial demonstrated that olaparib significantly prolonged PFS compared to placebo during maintenance phase therapy while maintaining the GHS of the patients involved without exposure to the toxicities of standard maintenance chemotherapy (5-FU or FOLFIRI) (3,5). Given our ability to give chemotherapy for a limited duration, a need for less toxic maintenance therapies are imperative.

Olaparib may therefore represent a helpful targeted therapy for the subgroup of patients with BRCA mutant pancreatic adenocarcinoma. The original PRODIGE 4 study did not investigate maintenance treatments for those patients with stable disease. Patients received up to 12 cycles of FOLFIRINOX if they had response and/or stable disease; they were followed every 3 months until death (1). Those with clinically significant cytopenias and toxicities had doses reduced (1). However, given the toxicities of FOLFIRINOX, maintenance therapies are actively being investigated to reduce toxicities and improve QoL. The PRODIGE 35-PANOPTIMOX study investigated three arms of treatment: arm A received 12 cycles of FOLFIRINOX, arm B received 8 cycles of FOLFIRINOX followed by FU maintenance, and arm C received sequential treatment alternating FOLFIRI and gemcitabine every 2 months (7). While there was no statistical difference with OS, there was a trend towards improved median OS (10.1 *vs.* 11.0 months), and objective response rates (35% *vs.* 41%) in arms A and B, respectively (7). This is likely explained by the fact that patients in arm B ultimately received higher cumulative doses of oxaliplatin (7). Perhaps a maintenance strategy allows patient to preserve PS while receiving higher cumulative doses of treatment

and ultimately improved OS. A growing body of evidence collected from the PRODIGE 35 and POLO trails are demonstrating that active investigation of novel maintenance therapies is not untenable, especially, with respect to olaparib, given its tolerability and sustained QoL.

The last ten years of research has yielded tremendous improvements in QoL for patients with metastatic PC. The PRODIGE 4 study yielded first-line therapy that not only increases OS/PFS but is able to improve TUDD with respect to GHS, and therefore QoL. Recent studies with maintenance regimens, best demonstrated by PRODIGE 35, shows that we are able to give patients less chemotherapy while maintaining stable burden of disease. Most excitingly is the evidence demonstrated by the POLO study, showing that targetable therapy is able to significantly increase PFS compared to placebo without any significant decrease in QoL.

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