EDITORIAL

Management of Pancreatic Cancer During COVID-19 Pandemic: To Treat or Not to Treat?

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ABSTRACT

Pancreatic cancer is a very aggressive disease and survival remains dismal even with treatment. Currently, management of patients with pancreatic cancer has been complicated by the ongoing COVID-19 pandemic. Medical oncologists face the dilemma of whether to treat or to not treat these patients who are at high-risk of complications and even death from COVID-19. No current guidelines are available and our limited experience at this time makes it more difficult to manage these patients. Although we have general strategies available from experience in Italy, we need more treatment specific strategies to help mitigate risks of complications and toxicities from chemotherapy in order to protect our patients from COVID-19 as much as possible.

EDITORIAL

Pancreatic cancer (PC) has a dismal prognosis and is now the third leading cause of cancer-related deaths in the United States [1]. Most patients present with unresectable or metastatic disease with an abysmal 5-year-overall survival (OS) rate of only 7%. Even when surgery is feasible in 15-20% of the patients, the 5-year survival remains only about 10% [2]. Therefore, it is considered the most lethal malignancy of all major cancers. To date, only two chemotherapy combination regimens (FOLFIRINOX-folinic acid, 5-fluorouracil, irinotecan, oxaliplatin and gemcitabine plus nab-paclitaxel) have shown OS benefit in patients with metastatic disease but at the cost of increased toxicity [3, 4].

Management of cancer patients at this time is further complicated by the global coronavirus pandemic [5, 6]. It poses a moral and ethical dilemma for medical oncologists: continue giving cytotoxic drugs at the risk of immunosuppression and predisposing already at high risk patients to COVID-19 or to hold treatment with the risk of progressive disease that already has a grim prognosis to begin with leading to even poorer outcomes. With the rapidly evolving situation currently, we have no guidelines available and it is imperative to come up with suggestions to help mitigate risks while at the same time help medical oncologists come up with ways to continue safely treating their patients with PC.

Patients with cancer are at a higher risk in general because of myelosuppressive effects of treatment and their disease. In addition, COVID-19 infection in itself also causes lymphopenia, which further weakens the immune system. Therefore, if PC patients receiving chemotherapy agents that cause neutropenia and lymphopenia develop infection with COVID-19, they may have significantly higher mortality rates. In the PRODIGE/ACCORD trial with FOLFIRINOX, the incidence of grade 3 or 4 neutropenia was seen in 45.7% of the patients compared to 21% in the gemcitabine group ($p<0.001$) [3]. In the MPACT trial grade 3 or higher neutropenia was seen in 38% of patients in nab-paclitaxel plus gemcitabine group compared to 27% in the gemcitabine alone group. In a retrospective study of 53 patients with resected PC looked at if adjuvant chemotherapy and radiation caused severe lymphopenia and if this was associated with adverse outcomes. This study reported that total lymphocyte counts (TLC) were normal in 91% of patient before adjuvant chemotherapy (5-FU or gemcitabine based) or radiation and two months after treatment, 45% of the patients had TLC<500 cells/mm3 [4]. In addition, median survival in patients with low TLC was 14 months versus 20 months ($p=0.048$). Therefore, treatment induced lymphopenia was frequent, severe, and an independent predictor for survival in patients with resected PC.

We have very limited data for patients with cancer who develop COVID-19 infection. In a retrospective analysis including 1,572 COVID-19 cases, authors identified 18 patients with cancer [5]. Patients with cancer were observed to have a higher risk of severe events (intensive care unit admissions requiring mechanical ventilation or death) compared with patients without cancer, 39% versus 8% respectively. Moreover, 75% (3 out of 4) patients who underwent chemotherapy or surgery in the past month had a higher risk of clinically severe events compared to 43% of patient who did not receive chemotherapy or surgery. Therefore, it is very important for medical oncologists to strongly weigh risks versus benefits of continuing cytotoxic treatments for PC patients with the on-going pandemic [6].

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Abbreviations PC Pancreatic cancer; OS Overall Survival; TLC Total Lymphocyte Counts; ASCO American Society of Clinical Oncology;
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Recently, American Society of Clinical Oncology (ASCO) released strategies identified by the Italian Ministry of Health to prioritize treatments for patients with cancer during COVID-19 pandemic [7, 8]. They identified three groups:

- Group 1: patients who completed treatment or whose disease is under control
- Group 2: patients undergoing active treatment (neo-adjuvant or adjuvant) with curative intent
- Group 3: patients undergoing treatment for metastatic disease

For group 1, they recommend delaying visits and follow up appointments and use phone contact or telemedicine visit instead. For group 2, recommendations are to treat cancer within a "COVID-19 free" clinical pathway that reduces the risk of COVID-19 infection for all patients by following universal guidelines such as washing hands, social distancing, and staff wearing personal protective equipment. Finally, for group 3, they recommend delaying treatment if not compromising disease control. If decision is made to continue treatment then the "COVID-19 free" clinical pathway is recommended. For patients on oral therapy, physicians should provide drug supply for 2 or 3 courses with home monitoring and using telemedicine for toxicity management.

In addition, we suggest the following strategies to simplify chemotherapy regimens to both decrease the frequency of clinic visits as well as to decrease risk of neutropenia in patients with pancreatic cancer:

1. Use low dose fixed dose capecitabine 1000 mg twice daily on days 1 to 21 of 28 days for patients who are on oxaliplatin, irinotecan, and gemcitabine combinations. For example, can start adjuvant treatment with capecitabine and add other agents (oxaliplatin, irinotecan, and gemcitabine) at later time.
2. Delay adjuvant therapy for up to 12 weeks from day of surgery for patients who underwent recent surgery
3. Neoadjuvant therapy can be extended in order to delay elective surgery as long as patient is tolerating treatment and showing response
4. Switch weekly schedule to bi-weekly schedule for gemcitabine/cisplatin, gemcitabine/oxaliplatin, or gemcitabine/capecitabine
5. Omit bolus 5-FU to reduce risk of neutropenia
6. Using the OPTI- regimens as well experienced previously such as OPTIMOX and OPTINAB previously published
7. Using S-regimens as we published previously, such as S-GEMOX, S-GOLF.
8. Biweekly gemcitabine-capecitabine
9. Use of OnPro kit
10. Use of same-day neulasta if OnPro not available, as previously published with safety and feasibility
11. Adopting to short infusion time for few drugs based on pharmacology
12. Consider home delivery of supportive medications so patients do not have to go outside to pick it up from their pharmacy
13. Can delay bisphosphonates doses if possible

Patients with cancer are at increased risk for poor outcomes from the on-going COVID-19 pandemic and are considered high-risk group. Limited data suggests close to 40% rate of adverse events, complications, and even death from COVID-19. At the same time, pancreatic cancer is a very aggressive disease and even with treatment, outcomes remain poor. Therefore, taking care of PC patients with the on-going pandemic can be very challenging and decision to treat or not to treat becomes almost impossible. On one hand, goal is to protect this vulnerable population and at the same time not compromise survival or disease control. Medical oncologists need to use individualized treatment strategies to decrease frequency of clinic visits, using tele-health for toxicity management, and altering treatment regimens to reduce risk of neutropenia.

Conflicts of Interest

None of the authors have any conflicts of interest to disclose.

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