

Perspective

Quality of Life Issues and Treatment in Pancreas Cancer

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Patients with pancreatic adenocarcinoma face many quality of life issues. Prior to the development of the FOLFIRINOX (5-FU, irinotecan, oxaliplatin, and leucovorin) [1,2] and gemcitabine/nab-paclitaxel [3] chemotherapeutic regimens the survival of patients with metastatic disease was on the order of 6 months. These two newer regimens increased the overall survival to an average of 11.1 and 8.5 months, respectively. Quality of life should be stabilized at the highest possible level with chemotherapy to postpone deterioration in functional status [4]. It has also been shown that pain and tiredness are independent survival prognostic indicators [5]. For these reasons, treatment for pancreatic cancer must take into account quality of life measures.

Gemcitabine became the standard of care for metastatic pancreas cancer following the pivotal trial comparing gemcitabine vs. 5-FU. Even though overall survival was approximately six months, 18% of the patients treated with gemcitabine were alive at one year compared to 2% in those patients treated with 5-FU. Clinical benefit (defined by pain control, Karnofsky performance status, and weight gain) was observed in 23.8% of gemcitabine treated patients versus 4.8% of those patients treated with 5-FU [6]. In the metastatic setting, fixed dose gemcitabine (1000 mg/m² weekly at a rate of 10 mg/m²/min) is preferred given the suggestions of increased efficacy although at the cost of increased hematologic side effects (neutropenia/ thrombocytopenia). Mild side effects such as nausea, emesis, and diarrhea are seen in less than 20% of patients [7]. In good performance status patients, doublet therapy is well tolerated, but in poor performance status patients gemcitabine is the standard of care [8]. With this being said, gemcitabine is usually well tolerated. Side effects such as a flu-like syndrome can occur, but the important rare side effect to watch for is gemcitabine associated thrombocytopenia purpura. This condition mimics traditional thrombocytopenia purpura [9-11]. There is some suggestion that the decrease in the tumor marker CA 19-9 may predict for better quality of life measures in the setting of gemcitabine therapy [12]. Recently, it was also shown that gemcitabine may also be responsible for a slight slowing of the functional decline of pancreas cancer patients [13].

Multiple agents have been tried in combination with gemcitabine. A more recent chemotherapeutic combination shown to have efficacy in pancreas cancer and have a FDA approval for metastatic disease is a combination of gemcitabine and erlotinib (epidermal growth factor receptor (EGFR) inhibitor) [14]. However, the overall survival benefit from the trial is on the order of 2

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weeks, and the quality of life on erlotinib is significantly reduced due to gastrointestinal toxicities such as diarrhea and a rash that is typical for EGFR inhibitors [15]. Given the decrease in quality of life and cost for a questionable increase in survival, these toxicities have led to questions of whether erlotinib is an appropriate choice of chemotherapy for the metastatic pancreas cancer patient [16,17].

The next major advance in pancreatic chemotherapy treatment was FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin). Even though 30% of patients respond to this regimen, FOLFIRINOX is intolerable in a large number of patients secondary to copious diarrhea, and neutropenic fever. In a single institution review from Yale University, 83% of patients required dose reductions in the first cycle due to toxicities [18]. The regimen is made more tolerable when the bolus 5-FU is removed from the regimen and pegfilgastrim is added to decrease the rate of febrile neutropenia and gastrointestinal toxicities [19]. Toxicities were alleviated at The Ohio State University by a modified regimen reducing the bolus dose of 5-FU, leucovorin and the initial dose of irinotecan while adding pegfilgastrim to the combination [20]. Chemotherapy such as FOLFIRINOX decreases the quality of life in patients with metastatic pancreas cancer as compared with gemcitabine. Notable areas were global health status, physical conditioning, cognitive functioning, social functioning, fatigue, and nausea/vomiting [21]. In addition, serious infections have occurred with this regimen and case reports have described concurrent invasive aspergillosis and pneumocystis pneumonia with the use of FOLFIRINOX [22]. After six months of therapy in good performance status patients, 66% of gemcitabine-treated patients had degradation of quality of life as measured by the QLQ-C30 scales as compared to 31% of patients treated with FOLFIRINOX. During the first eight

cycles, the patients receiving FOLFIRINOX had noticed increased diarrhea but other measures such as appetite loss, pain, dyspnea remained the same between the two groups [2]. Gemcitabine in combination with nab-paclitaxel achieves an overall survival in that is intermediate between gemcitabine and FOLFIRINOX [3]. Given its toxicity profile, it may represent a better choice in poorer performance status patients with advanced disease who are still candidates for doublet chemotherapy. Therefore, patients should be carefully selected for FOLFIRINOX therapy and the choice of chemotherapy needs to be individualized for each patient and their goals in treatment.

Quality of life in pancreas cancer while undergoing treatment is also affected by cachexia, pain and depression. Cachexia appears to be secondary to the biology of pancreatic cancer. For example, muscle wasting is known to be a direct effect of pancreatic cancer on the muscle microenvironment [23]. Therapeutics such as megestrol acetate can improve appetite and result in weight gain [24]. However, these agents do not reverse the cancer biology leading to symptoms of cachexia such as muscle wasting. The cancer anorexia-cachexia syndrome is an area of active research and other agents that are being explored include cytokine inhibitors and anti-inflammatory agents [25].

Quality of life is decreased by pain and depression prior to surgery or chemotherapy in newly diagnosed pancreas cancer [26]. The cause of pain in pancreatic cancer can be in part secondary to perineural invasion by the cancer [27]. Pain control in the case of the tumor in the area of the celiac plexus may be improved when pain is initially controlled with medication followed by celiac plexus block [28]. It is important to find the underlying etiology of what is causing the person pain and treat the cause to the best of one's ability. In one small study, quality of life measures were unchanged with home nurse visits as compared to traditional physician office visits, but patient's satisfaction increased [29]. Other quality of life issues including but not limited to gastric outlet obstruction, biliary obstruction and pancreatic insufficiency must all be addressed by the oncologist.

In conclusion, it is possible to administer chemotherapy and improve the quality of life for our patients with advanced pancreatic cancer. The performance status of the patient and determination of the overall goal of care is crucial in selecting the appropriate chemotherapy regimen.

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