

HIGHLIGHT ARTICLE

Metastatic Pancreatic Cancer: The Dilemma of Quality vs. Quantity of Life

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Summary

Due to pancreatic cancer's dismal prognosis, much of management is focused upon palliation and symptom management, and the decision to treat a patient with more aggressive maneuvers must always take into account the impact upon a patient's quality of life. In addition, majority of the patients with advanced pancreatic cancer are elderly. Oncologists are challenged to make tough treatment decisions. Many elderly patients cannot tolerate side effects of chemotherapy, especially the combination regimens. Despite that many patients continue to receive chemotherapy even in the last month of their lives. The effect of referral to palliative care on health-related outcome especially for patients with poor quality of life is still not very clear. The authors will review abstracts that have focused on these fields that were presented at the Annual Meeting of ASCO 2013 (Abstracts #4009, #4053, #6607, #9518, #9538, #9539, #9546, and #9638).

Introduction

In 2012, about 44,000 patients were diagnosed with pancreatic cancer in USA. At the same year about 38,000 patients have died because of pancreatic cancer [1]. Majority of pancreatic cancer patients are diagnosed with metastatic disease with very poor prognosis [2].

Chemotherapy for the metastatic pancreatic cancer has been single agent gemcitabine for patients with poor performance status or intensive chemotherapy regimen of FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, leucovorin) for those who with great performance status [3]. Majority of pancreatic cancer patients are older than 65 years of age [4]. Oncologists have to make difficult predictions on whether elderly patients with metastatic pancreatic cancer are able to tolerate any type (and what type) of chemotherapy, as this cohort of patients have multiple comorbidities, experience functional decline and inadequate calorie intake. Patients who are candidates to receive chemotherapy should be referred to palliative care.

Key words Palliative Care; Pancreatic Neoplasms; Quality of Life

Abbreviations FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, leucovorin)

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What Did We Know Before the 2013 ASCO Annual Meeting?

Pancreatic cancer is one of the most lethal malignancies. The distressing symptoms people with pancreatic cancer experience heighten the importance of early palliative-care intervention. At diagnosis patients often present with fatigue, loss of appetite, impaired sense of well-being, and pain. Patients with a localized cancer most commonly present with jaundice, while those with locally advanced or metastatic disease more likely present with abdominal pain and weight loss. Other problems include intestinal obstruction, biliary obstruction, pancreatic insufficiency, anorexia-cachexia and depression. Unfortunately, the current literature does not suggest a clear palliative role for chemoradiation and chemotherapy alone. As a physician taking care of these patients it is essential to know these symptoms and treatment modalities. Pancreatic cancer is a model illness to learn the palliative and supportive management in cancer patient. It is important for oncologists to recognize the importance of control measures and supportive measures that can minimize the symptoms of advanced disease and side effects of cancer treatment.

What Did We Learn at the 2013 ASCO Annual Meeting?

We will review abstracts presented in 2013 ASCO Annual Meeting on potential chemotherapies

that might be useful for elderly patients, palliative care vs. chemotherapy at the end of life and finally importance of quality of life at baseline for health-related outcome.

Potential Chemotherapies That Could Be Tolerable for Elderly Pancreatic Cancer Patients

In recent years more oncologists are using single agent gemcitabine for treating elderly patients with metastatic pancreatic cancer compared to 15 years ago [5]. In order to improve the outcome, many clinical trials have looked into combining gemcitabine with other agents. While overall these combinations have resulted in slight increase in overall survival, but the associated increased toxicity has limited their use in elderly metastatic cancer patients [6]. Elderly cancer patients in general receive less aggressive treatment than younger patients. In a retrospective study on 277 metastatic pancreatic cancer patients treated between 2000 to 2009, Vijayvergia *et al.* (Abstract #9546) found out that elderly patients (median age: 73.5 years) were less likely to receive any chemotherapy compared to younger patients (median age: 58 years) with HR=0.33 (P=0.001). Even those who have been treated were less likely to receive more than one drug (OR=0.48; P=0.003) [7]. Many would argue that elderly frail patients will not be fit enough to receive chemotherapy; however, as authors mention, younger and older patients were similar in their performance status. Moreover, although older pancreatic cancer patients had more cardiovascular comorbidity, cardiovascular comorbidity only had negative impact on overall survival of younger patients.

On the other hand, although majority of oncologists avoid using FOLFIRINOX in elderly pancreatic cancer patients, the study by Cartwright *et al.* (Abstract #6607) from the US Oncology Network shows that 24% of metastatic pancreatic cancer patients have received FOLFIRINOX (up from 13% a year before) while 76% of patients received gemcitabine (down from 87%). Those who received FOLFIRINOX had better overall survival compared to those who received just gemcitabine. Surprisingly half of patients who have received FOLFIRINOX were older than 67 years of age [8]. Despite this data, there are still many oncologists who are hesitant to administer FOLFIRINOX to elderly pancreatic cancer patients as shown by the first paper, so there is a critical need for other less toxic but effective drugs that can be combined with gemcitabine. This was the basis for the study by Strumberg *et al.* (Abstract #4009) that investigated the addition of anti-EGFR monoclonal antibody (nimotuzumab) to gemcitabine [9]. In this study 192 patients were randomized to either gemcitabine alone or gemcitabine 1,000 mg/m²

weekly in a 3-week cycle with nimotuzumab 400 mg weekly. In patients older than 62 years, the combination resulted in median overall survival and progression free survival of 8.8 and 5.5 months compared to just 5.2 and 3.2 months for gemcitabine, respectively. The combination was well tolerated with no grade 3/4 toxicity.

Chemotherapy vs. Palliative Care at the End of Life

Despite recent finding on role of palliative care at the end of life for cancer patients, still many patients receive chemotherapy at the end of life [10]. Two studies looked into chemotherapy at the end of life in the 2013 ASCO Annual Meeting. In the first study Rodriguez *et al.* (Abstract #9538) found out that among 5,607 patients treated at MD Anderson Cancer Center, Houston, TX, USA, from 2010 to 2012, only 4.6% of all metastatic cancer patients received chemotherapy at the end of life (within 14 days of death) while this rate was 4.2% for metastatic pancreatic cancer patients. Older age and comorbidity were associated with less chemotherapy at the end of life [11]. In second abstract Burke *et al.* (Abstract #9539) found that significant majority (98.6%) of these patients received standard agents [12].

The effectiveness of earlier referral to palliative care has been investigated by Raymond Jang *et al.* (Abstract #9518). Among 6,076 advanced pancreatic cancer patients, 52% of patients received palliative care consultation during their cancer care. Having just one palliative care visit was associated with fewer ICU admission near death (OR=0.25, 95% CI: 0.13-0.46), emergency room visit (OR=0.44, 95% CI: 0.33-0.58), and hospitalizations (OR=0.47, 95% CI: 0.33-0.69) at the end of life. Fewer patients who had follow up with palliative care following initial consult received chemotherapy at the end of life compared to those who were not referred to palliative care or did not follow up with palliative care after initial consultation (OR=0.26, 95% CI: 0.14-0.51) [13].

Impact of Performance Status on Quality of Life

Pancreatic cancer patients develop symptoms more frequently than other cancer patients. In a study looking into symptom clusters of 922 patients who have been referred to palliative care program, 83% and 32% of pancreatic cancer patients were fatigued or had upper gastrointestinal symptoms, respectively which were highest among all cancer subtypes (Abstract #9638) [14]. These symptoms may affect patients' quality of life at the time of diagnosis, which according to study by Vickers *et al.* (Abstract #4053) can predict survival. In the study on comparing gemcitabine and erlotinib vs. gemcitabine alone, 220 patients (out of 284) had baseline quality of life measurement by EORTC QLQ

C-30. Patients with better physical function domain of quality of life had longer overall survival compared to those with worse quality of life. (HR=0.91, 95% CI: 0.83-1.00). Those with better performance status (PS=0/1) had lower incidence of grade 3 or more toxicity compared to those with poor performance status (PS=2) (HR=0.36, 95% CI: 0.17-0.77) [15].

Discussion

Majority of patients with metastatic pancreatic cancer are older than age 65 years. Treatment decision making in this population is challenging for many oncologists due to lack of data. In the hallmark study of comparing FOLFIRINOX and gemcitabine, out of 342 patients, only 76 patients were 65 years or older. In these carefully selected elderly patients receiving FOLFIRINOX was associated with significant improvement in overall survival. (HR=0.48, 95% CI: 0.30-0.77). However, this regimen was associated with higher level of toxicity [16]. In order to assess whether there is tradeoff between prolonging life and maintaining quality of life, patients in the mentioned trial completed quality of life assessment by EORTC QLQ C-30 at baseline and every 2 weeks. The end point was time until deterioration which is measured by length of time that patient's quality of life declines by 10 or 20 points based on EORTC QLQ C-30. In this study patients in FOLFIRINOX arm experienced less and slower decline in many domains of their quality of life compared to patients in gemcitabine arm [17]. It seems that based on this data, the use of FOLFIRINOX has increased over the past 2 years [8]. There has been various studies looking into gemcitabine in combination with other agents [18]. As of now single agent gemcitabine or its combination with cetuximab or capecitabine are acceptable for older patients or those with poor performance status. While it is encouraging to see the benefit (and low toxicity profile) of adding nimotuzumab to gemcitabine for patients aged older than 62 years, further larger studies are needed to confirm this finding. It is still important to emphasize that patient age alone should not be a factor in treatment decision making. There has been emerging evidence on role of geriatric assessment in predicting chemotherapy toxicity in elderly cancer patients [19].

In recent years more attention has been paid to better symptom control in patients with advanced cancer diseases by earlier referral to palliative care services. In hall mark study in patients with advanced lung cancer, earlier referral to palliative care with standard oncological treatment resulted in improvement in quality of life and survival [20]. Surprisingly despite poor prognosis of metastatic pancreatic cancer, very few studies have looked into

role of palliative care in this setting [21, 22, 23] and significant proportion of metastatic pancreatic cancer patients receive chemotherapy in last 4 weeks of their lives [24]. The Abstract #9518 by Jang *et al.* [13] is one of first studies in this setting that has provided evidence on benefit of earlier referral to palliative care by reducing hospitalization and ICU admissions. Future studies should focus on barriers for early referrals to palliative care in this setting.

In recent years quality of life of metastatic cancer patients have got more attention. A meta-analysis on 30 randomized controlled trials (including one randomized controlled trial in metastatic pancreatic patients), baseline quality of life especially physical functioning, pain, and appetite loss increased the accuracy of overall survival predictive model when added to other clinical and socio-demographic factors [25]. The Abstract #4053 by Vickers *et al.* [15] are in agreement with finding of the meta-analysis. One worthy question is whether quality of life of patients with poor quality of life at baseline improves if they respond to pancreatic cancer treatment or not? From limited data it seems the answer is no. Analysis of 186 patients who completed baseline and follow-up quality of life questionnaires who were either receiving gemcitabine/placebo or gemcitabine/bevacizumab showed that response to treatment does not correlate significantly with improvement in quality of life [26]. Oncologists should be aware of the data that patients with poor quality of life have even poorer response to chemotherapy, and even if their tumor respond, that does not necessarily leads to improvement in their quality of life.

Conflict of interest The authors have no potential conflicts of interest

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