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HIGHLIGHT ARTICLE

Use of Supportive Care for Symptom Management in Pancreatic Cancer: Application of Clinical Research to Patient Care

Highlights from the "2012 ASCO Annual Meeting". Chicago, IL, USA; May 31 - June 5, 2012

Meropi Panagiotarakou[1], Anumeha Gupta[2], Kostas Syrigos[1], Muhammad Wasif Saif[3]

[1]Oncology Unit, Sotiria General Hospital, University of Athens. Athens, Greece. [2]Hematology Oncology and [3]Department of Medicine and Cancer Center, Tufts University Medical Center. Boston, MA, USA

Summary

In this paper, we will be discussing Abstracts #9061, #9062, #9065, #9072 and #9097 presented at the recent 2012 American Society of Clinical Oncology (ASCO) Annual Meeting. All of these abstracts explore innovative ways to control symptoms in cancer patients. We are hopeful that these methods are able to be used in symptomatic pancreatic cancer patients.

What we Knew Before the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting

Pancreatic cancer is one of the most aggressive malignancies, as it is the fourth and sixth leading cause of cancer death in the United States and Europe, respectively. Despite many advances in diagnosis, therapy and palliation of pancreatic cancer, the overall survival of affected patients is still dismal [1]. Clinical manifestations of pancreatic cancer include pain, weight loss, anorexia cachexia syndrome, fatigue, nausea, vomiting, steatorrhea, dyspepsia, pruritus, jaundice, depression and deep venous thrombosis [2]. Toxicities and adverse events of chemotherapy should also be taken into account. Thus, affected patients require early and frequent palliative and supportive care, in order to achieve the improvement in quality of their life, regardless of their treatment status. Management of pancreatic cancer related symptoms has been a challenge for the oncological community. Efforts are underway in identifying palliative measures in this patient population that could also be cost effective [3].

In this article, we will attempt to describe findings from key abstracts presented at the recent ASCO 2012 Annual Meeting relating to supportive care in patients with cancer.

Keywords Cachexia; Melatonin; Methylphenidate; Palliative Care; Pancreatic Neoplasms; Vitamin D

Correspondence Muhammad Wasif Saif
Department of Medicine and Cancer Center; Tufts Medical Center; 800 Washington Street Box 245; Boston, MA 02111; USA
Phone: +1-617.636.8077; Fax: +1-617.636.7060
E-mail: wsaif@tuftsmedicalcenter.org

What We Learned at the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting

Cancer Related Fatigue and Cachexia

Escalante *et al*. (Abstract #9072) studied the effects of extended release OROS® methylphenidate (Janssen Pharmaceuticals, Titusville, New Jersey, USA) on common cancer symptoms in 33 breast cancer patients [4]. The primary end point of the study was cancer related fatigue and secondary endpoints included cognitive function, ability to work at a job and patient perceptions. The study population was randomly divided into two groups, one receiving OROS® methylphenidate and the other receiving placebo.

Table 1 shows the characteristics of patient population in this study. After two weeks on treatment, the groups were allowed to crossover. The primary endpoint was evaluated at baseline, two weeks and 4 weeks using

Table 1. Characteristics of the patient population of a study on the effects of extended release OROS® methylphenidate on common cancer symptoms in 33 breast cancer patients (Escalante *et al*., Abstract #9072) [4].

Mean age (range); years	58 (32-79)
Patients with metastasis	30%
Patients receiving chemotherapy	82%
Patients receiving hormonal therapy	9%
Patients receiving hormonal plus chemotherapy	9%
Patients with ECOG status less than 1	94%
Patients employed	54%
Patients requiring pain medications	45%
Mean baseline score for cancer related fatigue (range)	5.7 (4.1-8.6)

ECOG: Eastern Cooperative Oncology Group

Brief Fatigue Inventory (M.D. Anderson Cancer Center, Houston, TX, USA). Cancer related fatigue and other symptoms did not show statistically significant improvement between the two groups (P=0.54). Other secondary measures, such as work attendance and cognitive function, did show statistically significant improvement in patients who took methylphenidate. Patients reported high rates of subjective improvement while on methylphenidate and a high percentage also wanted to continue given the excellent tolerability of the drug. The authors also recorded the serum cytokine levels, but not conclusive data could be drawn.

It appears that while fatigue was not well controlled, patients on methylphenidate had an improved overall quality of life with minimal side effects from the drug. We believe this is a worthwhile strategy to use in pancreatic cancer patients who would like to optimize the quality of their lives.

The potential use of vitamin D and its analog in the prevention and treatment of cancer symptoms is an area under investigation. The effect of vitamin D supplementation on cancer-related fatigue in patients who had not received prior chemotherapy was studied by Trivanovic *et al*. (Abstract #9097) [5]. Sixty-nine patients with vitamin D deficiency participated in this prospective 3-month study. Patients were randomly divided into those receiving vitamin D3 daily for 3 months during their treatment and those continuing their standard treatment without vitamin D3 supplementation. Patients were eligible if the life expectancy was equal to, or greater than, 6 months, Eastern Cooperative Oncology Group (ECOG) performance status was between 0 and 3, the serum 25-hydroxyvitamin D3 was low (cutoff value 32 ng/mL) and serum calcium level was normal. The measurement of cancer-related fatigue was based on the Functional Assessment of Cancer Therapy Fatigue module (FACT-F: www.facit.org). The primary measured endpoint was the changes in the FACT-F scale. The secondary endpoints were the improvement of vitamin D serum levels and safety. In this study, vitamin D3 supplementation showed statistically significant improvement in fatigue ($P<0.05$) and corresponding increase in serum vitamin D levels ($P<0.001$) between the experimental and control groups. Both groups had similar grade 3 and 4 adverse events. Vitamin D appears to be a useful adjunctive therapy according to this small prospective study. This study certainly warrants a larger prospective randomized trial. In the meantime, vitamin D is cheap and easily available and given the acceptable safety profile can be offered to cancer patients with low vitamin D levels.

Melatonin has been utilized to treat cancer related symptoms including fatigue, weight loss and depression. It has also been used with mixed results in the treatment of cachexia. This trial by Del Fabbro *et al*. reported in Abstract #9062 attempted to evaluate the utility of melatonin in controlling cancer related cachexia by designing a randomized controlled trial [6]. Patients with advanced lung or gastrointestinal cancer; appetite scores greater than 3 on a scale of 0 to 10 (with 10 being the worst); weight loss equal to, or greater than, 5% within 6 months were eligible to participate in the trial. Symptoms were assessed using the Edmonton symptom assessment scale and quality of life was measured using functional assessment of anorexia/cachexia therapy. The trial was stopped early when an interim analysis done on 48 patients showed no difference in symptom control or quality of life. The authors concluded that melatonin does not have an effect on controlling cancer related symptoms in patients with advanced disease.

Nausea and Vomiting

Despite use of excellent drugs to control chemotherapy induced vomiting, our current arsenal is limited in controlling patient reported nausea. Although nausea and vomiting are often reported together, these are two different clinical entities that require different treatment modalities. While emesis is an objective finding, nausea is entirely subjective and therefore highly variable. Often, agents that are able to control emesis are only moderately successful at controlling nausea. We report findings of a small randomized trial reported in Abstract #9061 from Grunberg *et al.* designed to evaluate the use of dronabinol, a cannabinoid agent in controlling nausea [7]. Adults with solid tumors receiving doxorubicin at a dose equal to, or greater than, 40 mg/m^2 or cyclophosphamide at a dose equal to, or greater than, 1,500 mg/m^2 or who had also received mildly emetogenic chemotherapy on a prior occasion were eligible to participate in the trial. Patients were not eligible if: they were receiving other moderately or highly emetogenic chemotherapy; undergoing cranial, abdominal or pelvic radiation; had experienced chemotherapy induced vomiting or chemotherapy induced nausea with prior chemotherapy; had other causes of nausea and vomiting; had been receiving other antiemetics; or were habitual cannabinoid users. Sixty-two patients were eligible and all received 10 mg of i.v. dexamethasone and 0.25 mg of palonosteron. Patients were than randomized to the treatment arm and placebo arm. The treatment arm received dronabinol 5 mg by mouth three times a day for 5 days. Relevant data documenting nausea, vomiting and drug toxicity was collected during the 5 days. Table 2 shows the patient demographics.

Table 2. Patient demographics of a small randomized trial designed to evaluate the use of dronabinol in controlling nausea (Grunberg *et al*., Abstract #9061) [7].

Sex:	
- Male	1 (1.6%)
- Female	61 (98.4%)
Race:	
- White	45 (72.6%)
- Black	14 (22.6%)
- Hispanic	2 (3.2%)
- Other	1 (1.6%)
Age: mean (range)	58 years (29-76)

Table 3. Results of a small randomized trial designed to evaluate the use of dronabinol in controlling nausea (Grunberg *et al*., Abstract #9061) [7].

	Dronabinol	Placebo	P value
Duration of nausea	1.86 days	3.10 days	0.027
No nausea	37%	17%	0.143

No differences were noted with respect to chemotherapy induced vomiting. However differences were noted with respect to nausea. Table 3 summarizes the results.
The authors concluded that dronabinol has a role in controlling chemotherapy induced nausea and could be used with drugs like dexamethasone and serotonin receptor antagonists like ondansetron.

Role of Palliative Care in Comprehensive Cancer Care

Supportive treatment should not only be offered to cancer patients in the late stages of the disease. It should be part of multidisciplinary approach at the initiation of the treatment. Kwon *et al*. (Abstract #9065) evaluated the clinical characteristics, symptoms and service utilization between patients with expected survival equal to, or greater than, 2 years or receiving curative treatment (early referrals) *versus* other cancer patients (late referrals) referred to a supportive care clinic [8]. The patient cohorts were selected from a single supportive care clinic. The patients also had to have a follow-up visit within 30 days between August 2008 and October 2010. Of the 1,208 patients reviewed, 695 patients were documented to have a return visit within 30 days of the previous visit. Of the 695 patients, 100 (14.4%) were able to be categorized as early referrals and another 100 patients were randomly selected from the pool of 695 patients and classified as late referrals. Baseline symptoms were similar between the two groups with the exception of insomnia which was noted to be statistically significant in the late referrals group.

Table 4. Results of a trial evaluating the clinical characteristics, symptoms and service utilization between patients with expected survival equal to, or greater than, 2 years or receiving curative treatment (early referrals) *versus* other cancer patients (late referrals) referred to a supportive care clinic (Kwon *et al*., Abstract #9065) [8].

Characteristics measured	Referrals		P value
	Early	Late	
Median age (years)	54	60	0.009
Head and neck cancer	67%	6%	<0.001
1st visit since the initial diagnosis (months)	3.8	16.2	<0.001
CAGE positive [a]	15%	4%	0.014
Referred from radiation therapy clinic	49%	3%	<0.001
Referred for treatment-related side effects	70%	48%	0.0002
Insomnia score	1.8	2	0.004
Improvement in symptom distress score	-5.5	-3	0.007
Overall median number of visits	24	2.1	0.007
Median visits per month	2.1	4.3	<0.001

[a] Authors do not specify in the abstract if they checked the gene or the protein product the patients.

Table 4 summarizes the results. Early referral in this patient population resulted in decreased number of clinic visits per month with improvement in symptom burden. Furthermore, patients who were late referrals to the supportive care clinic also benefited greatly from symptom relief.

Conclusion

Supportive care in oncology is a highly evolving field. These abstracts presented at 2012 ASCO Annual Meeting support the use of unique modalities in controlling symptoms and also highlight the importance of ongoing research. Patients with advanced pancreatic cancer usually present with a high symptom burden and it is imperative that a multidisciplinary approach involving palliative care should be taken at the onset of care. The findings presented in these abstracts offer new and exciting approaches to symptom management in our patients including management of nausea and cancer related fatigue. Open communication regarding symptom management should be part of every clinic visit for these patients. Given the short duration of survival in patients with advanced pancreatic cancer, quality of life needs to be optimized. We believe further research is necessary in order to provide better care for cancer patients in general and pancreatic cancer patients in particular.

Conflict of interest The authors have no potential conflicts of interest

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