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The Emergency Care of Patients With Cancer: Setting the Research Agenda

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Abstract

To identify research priorities and appropriate resources and to establish the infrastructure required to address the emergency care of patients with cancer, the National Institutes of Health's National Cancer Institute and the Office of Emergency Care Research sponsored a one-day workshop, "Cancer and Emergency Medicine: Setting the Research Agenda," in March 2015 in Bethesda, MD. Participants included leading researchers and clinicians in the fields of oncology, emergency medicine, and palliative care, and representatives from the National Institutes of Health. Attendees were charged with identifying research opportunities and priorities to advance the understanding of the emergency care of cancer patients. Recommendations were made in 4 areas: the collection of epidemiologic data, care of the patient with febrile neutropenia, acute events such as dyspnea, and palliative care in the emergency department setting.

INTRODUCTION

In the United States, there are more than 14 million people who have been treated for cancer at some time in their lives.[1] Of these, more than 5 million are within 5 years of their original diagnosis, and the burden of illness can be overwhelming to patients. Acute symptoms are common, including breakthrough pain, gastrointestinal adverse events, dyspnea, and infection, and they create an urgent need for treatment. Although the majority of cancer treatment is delivered in outpatient settings, patients with complications are often treated in the emergency department (ED).

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In March 2015, the National Cancer Institute and the Office of Emergency Care Research sponsored a 1-day workshop, titled “Cancer and Emergency Medicine: Setting the Research Agenda,” in Bethesda, MD. The goal of the workshop was to identify research opportunities and determine research priorities for issues related to the emergency care of the cancer patient. Twenty-six participants attended and were invited according to their previous work in the field or on the recommendation of others. Their backgrounds were emergency medicine (8), oncology (3), internal medicine (1), oncologic EDs (4), operations (1), and palliative care/emergency medicine (3). In addition, federal attendees represented the National Cancer Institute (4), the National Institute of Nursing Research (1), and the Office of Emergency Care Research.

WORKSHOP FINDINGS

National Data on Cancer Care in the ED

There are two nationally representative databases, the National Hospital Ambulatory Medical Care Survey and the Nationwide Emergency Department Sample, which can be used to gauge the scope of cancer care in EDs nationally. Unpublished analyses of these data suggest that patients with cancer make up approximately 3% of all ED visits and that the admission rate for this group of patients is much higher than that of the general ED population.

Obtaining accurate data about the use of the ED by patients with cancer is hampered by the lack of consensus definition of “a patient with cancer” in the emergency setting. This is the cornerstone of identifying the appropriateness of data elements currently available in public data sets. Currently, a “patient with cancer” might include a person undergoing active cancer treatment, including surgery, radiation, targeted therapy, or chemotherapy, at any stage of illness. It may also include a patient with a remote diagnosis of cancer that is either cured or is in remission who is at risk for treatment-related late effects and cancer recurrence. A uniform definition for reporting is therefore needed.

Cancer patients in the ED can be identified with administrative diagnostic codes, but there are several methodological concerns with accurate case ascertainment. “Rule-out” codes, common in administrative data sets, can be misleading for classification purposes. The reliability of these codes and the agreement of how to code diagnoses across providers are other factors that need to be explored. To allow uniformity of reporting, consensus on these issues is of key importance, as is harmonization of all data elements describing ED utilization by cancer patients with those of other common data sets (such as those supported by National Cancer Institute and the National Institute of Nursing Research).

Research recommendations: national data

- ED use by cancer patients: Understanding how cancer patients use EDs is a critical first step in improving their care. Although the collection of quality epidemiologic data is expensive and time consuming, it may be possible to supplement existing surveys with cancer-specific fields. Additionally, a review of all currently available sources of data, including emergency visit–specific

databases, as well as broader resources such as the Surveillance, Epidemiology and End Results (SEER)-Meidcare database, should be conducted to explore feasibility and understand evidence gaps. Before implementing additional data collection, the community should address two important epidemiologic questions: the definition of a cancer-related ED visit and the definition of a cancer patient. Subsequent evaluation should focus on how these definitions may be harmonized with currently available data elements.

- Electronic medical records: With the near-universal adoption of electronic medical records, studies should address how to operationalize this record to better capture quality ED diagnostic data. These data should incorporate the status of cancer treatment and the reasons and ways in which cancer patients reach the ED. Quality data should highlight any cancer-related diagnoses, including treatment-related adverse events, to understand the roles that the health system, oncologist, and primary care physician play in directing or avoiding these ED visits.

- Options for ED care: Besides hospital-based EDs, the country is experiencing a rapid increase in the number of freestanding EDs,[2] and their role in the treatment of cancer patients should be part of the research efforts. Another important change in the emergency care of cancer patients is the creation of cancer-specific EDs, which may serve a hospital-based cancer center or a multispecialty hospital in which cancer care is only one of the services it provides. The relationship between the patient populations and quality of care within cancer- specific EDs in comparison to nonspecialized general EDs needs to be understood through the analysis of data generated from both of these areas. There are likely to be lessons gained from data collection and treatment protocols that compare these two clinical practice sites and can be translated into improved treatment. Finally, there needs to be a better understanding of the role of ED observation units in the care of cancer patients. All of these aspects of cancer patient care delivery in the ED are largely unknown, making this an area of novel priority for health care quality in both emergency medicine and oncology.

Febrile Neutropenia: Current Practice, Gaps in Evidence, and Barriers to Translation

Febrile neutropenia is a serious complication resulting from cancer treatments. It causes profound bone marrow suppression and leaves patients susceptible to serious bacterial and fungal infections.[3–6] It occurs in approximately 10% to 30% of chemotherapy-treated cancer patients (depending on several factors) and causes significant morbidity and mortality, with important long- term implications for the use of health care resources.[7–12] A recent national study of febrile neutropenia patients treated at 115 medical centers throughout the United States estimated an inhospital mortality rate of 9.5%, with a mean hospital duration of 11.5 days.[13] Because it is such a common condition, participants believed that febrile neutropenia required special focus in the workshop.

Guidelines developed by various national and international organizations to optimize the treatment of febrile neutropenia universally recommend the prompt initiation of antibiotic therapy for febrile neutropenia patients, which is usually defined as within 60 minutes of presentation.[14–20] Despite these recommendations, there are still significant delays in the administration of this critical treatment in EDs where febrile neutropenia patients frequently seek immediate medical care. Studies have illustrated significant delays in the timing of initial antibiotic treatment for febrile neutropenia patients, with a median ED time to initial antibiotics ranging from 102 to 300 minutes, which indicates a poor adherence with treatment guidelines.[20,21]

Although it seems intuitive that febrile neutropenia patients should receive their initial antibiotic treatment within 60 minutes of presentation to an ED, this goal is problematic for several clinical and operational reasons. But as has been shown in the cases of myocardial infarction[22,23] and stroke,[24] EDs are systemically capable of delivering rapid interventions. If beneficial outcomes of earlier initial antibiotic treatment are illustrated, it is likely that new operational efforts will be developed to improve the ED care of patients with febrile neutropenia. Because of the demands for emergency staff to provide rapid care to all patients with critical conditions, any operational strategy aimed toward reducing the time to initial antibiotic treatment must be based on convincing evidence of a positive clinical effect. Only then should it be integrated into the emergency care of patients with febrile neutropenia. Consequently, future guidelines and protocols recommending rapid antibiotic treatment for febrile neutropenia in EDs must be based on adequately powered and clinically valid studies that clearly indicate the effectiveness of this intervention. To date, only a few small studies have evaluated the effects of delayed timing of antibiotic therapy in adult patients with febrile neutropenia, and they found conflicting results.[25–28]

In addition, identification of patients at the highest risk of serious infections is a major challenge. Outcomes for both neutropenic and non-neutropenic patients with fever in the ED are a data source that might be used to build best practices for this population.

Research recommendations: febrile neutropenia

- Treatment of febrile neutropenia: Larger and more definitive clinical investigations should be conductedto identify optimal treatment strategies for febrile neutropenia patients in the ED setting, including the effects of the timing of initial antibiotic therapy. Early research questions aimed at understanding and improving the care of febrile neutropenia must first address the different definitions of febrile neutropenia, objective treatment response, and other conditions that are treated. Large studies should also investigate ED barriers that prevent the prompt administration of antibiotics; chief among these is the role of ED crowding. However, any research assessing the effects of early versus delayed initial antibiotic treatment should recognize that the severity of illness is a potential confounding factor; sicker patients are more likely to receive earlier antibiotics, and these patients also tend to have worse outcomes. This may lead to the erroneous conclusion that early antibiotic treatment causes worse outcomes. Therefore, properly conducted clinical

research must control for any potential confounding by severity of illness and, in addition, consider the effect of delay in presentation.

- Biomarkers and risk-stratification tools: Risk-stratification tools to predict the benefit of antibiotic treatment should be validated in the ED, and the role of biomarkers and other markers (such as procalcitonin) in risk stratification is another area for further research. Recently developed rapid diagnostic tests for the identification of febrile neutropenia patients with fungal infections should also be investigated for their effects on mortality and other patient-centered outcomes such as length of hospitalization.[29] Finally, advanced analytic techniques may have a role to play in predicting which patients are at highest risk in real time—as a function of cancer features, chemotherapy regimen, medical history, and other features in electronic health records—before the patient even has blood drawn to check for neutropenia.

ACUTE EVENTS IN ED CANCER CARE

Acute events are common in cancer but have not been a major focus of most data sources on the cancer disease trajectory, including large national registries. As a result, the significance of these events for the patient experience or the disease trajectory is not well understood. Workshop attendees identified many acute events that affect cancer patients and precipitate an ED visit—pain, infection, venous thrombosis, spinal cord compression, seizures related to brain lesions—and the knowledge gaps in several of these. These events can be managed in general EDs or so-called cancer EDs at major cancer treatment centers. A key theme that arose during the workshop is the complex task of diagnosing a new acute event in cancer patients, which must proceed concurrently with symptom palliation. Is the acute event known to be associated with the underlying cancer, or is it instead a symptom of a new and unrelated condition? In addition, it is unclear whether clinical rules accurately specify types of cancer patients. In regard to pulmonary embolus, for example, it is clear that different cancers have vastly different implications for risk of thromboembolic disease. However, a widely used decision rule simply incorporates one point for treatment for “active cancer,” whether that cancer is a localized melanoma or metastasized breast cancer.[30]

Of the many conditions that could be discussed, the workshop focused on two:

- Cancer-related pain. Pain can indicate impending decompensation because of a new complication or cancer recurrence, and both the pain and its cause require management.[31] Despite its importance, there is no consensus on the definition of “breakthrough pain,” and it is unclear which tools are the best to assess its severity. Patients with cancer-related pain often have a mixed type of pain, nociceptive and neuropathic, which makes it more challenging to treat. There are recommendations for the use of morphine, oxycodone, and hydromorphone in the setting of palliative care,[32] but to our knowledge no guidelines exist for acute or breakthrough pain in the ED. One promising direction of this research could be to learn from the treatment of sickle cell pain, for which EDs have developed best practices; can these be applied to cancer patients with pain, and how can patients be incorporated into decisionmaking? Are non-ED treatments

for breakthrough pain valid and feasible in the ED environment? Finally, is it possible to tailor analgesia to specific primary cancers?

- Acute dyspnea. This condition accounts for 12% of the chief complaints among cancer patients presenting to the ED (unpublished data). Dyspnea presents a set of problems similar to those of pain as both a bothersome symptom and a potential manifestation of a new life- threatening process. Preliminary data in the Medicare population were presented that show that pulmonary embolism is underdiagnosed in EDs and outpatient clinics, particularly in cancer patients—in whom it is often misdiagnosed as progression of underlying disease (unpublished data). Research recommendations: acute events.
- Treatment of acute pain: Work should be undertaken to determine the effect of cancer pain on ED utilization, which is an area that has not previously been addressed. Research is also needed into the barriers, skills, and attitudes of emergency care providers in the treatment of cancer pain, and whether there are racial or socioeconomic gaps in the treatment of pain in cancer patients. Research should also be focused on understanding which analgesics are best to treat acute cancer-related pain in the ED and how to improve coordination with outside providers to control breakthrough pain and reduce the need for an emergency visit.
- Dyspnea: Claims data should be explored to provide epidemiologic data and as a tool for predictive modeling. Research is also needed to reduce the misdiagnosis of pulmonary embolism in patients with cancer.
- Other research priorities: A large number of questions related to treatment of acute events are unanswered: What is the role for standard steroid regimens for patients with spinal cord syndrome? What is the best approach to starting antiseizure medications in the ED for cancer patients with known or suspected brain lesions? Although randomized trials would be ideal, the realities of cancer care suggest that these will be unlikely, and so rigorous studies using quasi-experimental methods are urgently needed to begin filling this gap. Finally, there are a number of questions related to acute spinal cord complaints, such as risk stratification for cancer patients presenting with back pain and the use of spinal magnetic resonance imaging.

Cancer Palliative Care in the ED: Health Care Use and Patient Management

Palliative care is a multidimensional approach to relieve the stress and suffering associated with illness. It incorporates the physical, spiritual, psychological, and social support provided to patients and families experiencing a serious, life-threatening illness, in which the

focus of care is the patient and their family and caregivers. In contrast, it is the patient alone who is the usual focus of care in the ED. The focus of palliative care is on optimization of quality of life and relief of the physical, spiritual, and psychological suffering that occurs during a serious illness. Palliative care should not be confused with hospice care, which is the type of palliative care that is provided when the patient has a terminal illness and a life expectancy of 6 months or fewer if the disease runs its usual course. It is the form of palliative care elected under a formal program for patients with terminal illness.

Exquisite attention to multidimensional suffering is key across the cancer trajectory. Patients with advanced cancer experience a large symptom burden and are likely to have an ED visit during the course of their illness.[33,34] Palliative care support can and should be provided at any stage of illness and can be provided congruently with any therapy.[35] The integration of palliative care and emergency medicine is crucial to improve the quality of care for patients with advanced cancer. There is an increasing number of emergency physicians who are also trained in palliative care, and the American College of Emergency Physicians' 2013 "Choosing Wisely" campaign already encourages the early referral of appropriate ED patients to palliative care or hospice. However, most EDs in the United States do not have access to a hospital-based hospice care service, although there are hospice providers in most communities. There is an increasing evidence base in palliative care and cancer, including high-quality evidence from clinical trials on the benefits of palliative care.[36–38] Despite the body of evidence about palliative care and oncology from research conducted in the ambulatory and inpatient setting, much less is known about what aspects of palliative care can and should be delivered in the ED. Although previous work has demonstrated substantial palliative care needs in ED patients,[39] a comprehensive assessment of the physical, psychosocial, and spiritual needs of patients and their family members takes substantial time. In addition, patients and family members may or may not be receptive to assessing goals of care and making changes to the treatment plan during a time of crisis. Despite this potential barrier, the ED visit represents a critical opportunity during which to connect patients and families to such support services.

Research recommendations for palliative care in the ED

- Quantitative research: The research in palliative care and oncology in this setting has been almost exclusively descriptive. More detail is needed, however, about the use of life-sustaining therapies and how and when to perform a rapid goals-of-care conversation with patients and their family members.
- Follow-up care: Connections to other out-of-hospital, ambulatory, and inpatient providers need to be elucidated and new disposition pathways need to be explored. Although successful ED-community hospice partnerships exist, they need broader replication and scaling. Further research needs to be undertaken in this area to ensure that clinicians and policymakers have sufficient information for service provision.

SUMMARY AND FUTURE DIRECTIONS

The ED provides care for many of the most seriously ill patients with cancer, and improving their care begins with asking the right research questions. The Office of Emergency Care Research and the National Cancer Institute are using the recommendations of the workshop to develop and shape their research agenda in the emergency care of the patient with cancer. After the workshop, the National Cancer Institute–supported Comprehensive Oncologic Emergencies Research Network consortium was formed. It will consist of approximately a dozen EDs that will take part in clinical studies. The network will begin some proof-of-concept studies soon.[40] These will focus on collecting epidemiologic data about the use of EDs by patients with cancer. We hope that steps such as these will further improve emergency care of the cancer patient.

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