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Feature Articles

Targeted therapy use in adults with cancer ≥85 years of age

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ABSTRACT

Purpose: Assess patient- and clinical-related variables associated with targeted cancer treatments (TTs) for adults ≥85 years of age.
Rationale: TTs have pathway-specific side effects that negatively affect QoL and medication adherence, which may reduce TT efficacy. Research has not focused on patients aged ≥85 years; therefore, the scope of TT use in this age group is not understood.
Methods: We conducted an electronic medical record review to identify individuals ≥85 years treated with TT.
Results: The sample ($N = 295$) was 53.5% male, 41% married/partnered, and 73.7% Caucasian. Common cancer types included breast (26.3%), prostate (31.3%), and leukemia (14.1%). Only one-third ($n = 98$) of the sample had TT side effects noted in their patient chart.
Conclusions: Patients aged ≥85 years took similar TTs and experienced similar side effects as reported by research of younger patients; however, symptom experience was not well-reported.

Introduction

As of 2016, twenty-one percent (21%) of all cancer survivors, defined as individuals with cancer from the time of diagnosis through end of life (including individuals undergoing treatment and those who are cancer-free), were over the age of 80 years.[1] From 2012 to 2050, the number of people aged ≥85 years is expected to increase from approximately 6000 to 18,000.[2] Moreover, the cost of cancer care in the U.S. is projected to rise to $173 billion by 2020[3] much of which will come from the care of older adults with cancer.[4]

The age that represents an older adult in cancer research varies from study to study, ranging from 65[5] to 70[6,7] to 75[8,9] years of age. In general, older adults (≥70) with cancer have been shown to benefit from traditional chemotherapy;[10,11] however, more than 90% of older patients with cancer experience moderate to severe toxicity with standard chemotherapy,[10] leading to suboptimal treatment and potentially decreased patient survival. Efforts to improve survival while maintaining quality of life (QoL) for patients with cancer have led to development of targeted therapies (TTs), which focus on treatment of specific pathways in cancer cells, while sparing normal cells, thereby increasing safety and therapeutic efficacy for patients with cancer.[12,13] Use of TT represents one of the growing number of approaches to personalized treatment of cancer, because in TT patients receive therapy based on the unique genetic profile, or subtype, of his/her cancer.[13] Examples of TTs include tyrosine kinase inhibitors (TKIs) such as erlotinib (Tarceva®; OSI Pharmaceuticals LLC, Northbrook, IL, USA; non-small cell lung cancer; NSCLC)[14] and imatinib mesylate (Gleevec®, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA: chronic myeloid leukemia; CML).[15]

Despite the growing number of cancer survivors over the age of 80 years, little research has focused on the use of TT in patients of extreme age. Generally, TTs are approved by the U.S. Food and Drug Administration for use in patients with cancer, including older adults, by demonstrating efficacy in prolonging patient survival, improving quality of life, or both.[16] For example, erlotinib has been demonstrated as an effective treatment for older adults, resulting in mild to moderate adverse events with good disease control.[8,17] However, this research is limited by exclusion or under-representation of older adults in clinical trials,[18] with few studies including participants ≥80 years of age.[6,19,20]

Some data suggest that there are age-related challenges for older adults with cancer that may affect their use of TT;[7,21–23] for example, older adults may respond differently to cancer treatment compared to younger adults.[24,25] In particular, there have been concerns about the safety of TTs in older adults.[22,23,26] TTs have unique, pathway-

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specific side effects that can increase symptom burden, decrease patient QoL, and lead to TT interruption or discontinuation[20,27,28] requiring patients and their caregivers to make a "trade-off" between treatment for a life-limiting disease and QoL. The purpose of this study was to expand on what is currently known about TT use in older adults and specifically to: 1) identify sociodemographic and patient-related variables associated with use of TT cancer treatment; 2) describe side effects of TT among older patients; and 3) describe the frequency, duration, and reasons for discontinuation of TT.

Materials and methods

This was a retrospective descriptive study. We reviewed electronic medical records of patients with cancer who had received TT over the past seven years (2010 to 2017). The study was approved by the University of Maryland, Baltimore Institutional Review Board (IRB). Data were collected from April 2017 to August 2017.

Sample and setting

This study included a mixed cancer population (i.e., solid tumors and leukemias/lymphomas). Older individuals were eligible to participate in the study if they were treated at a National Cancer Institute-designated comprehensive cancer center (urban) or an affiliated acute care hospital (suburban), if they were ≥85 years of age, if they had a histologically confirmed cancer (any type/stage), and if they took TT at some point in the past seven years. For the purposes of this study, TT included tyrosine kinase inhibitors (TKIs; e.g., erlotinib, lapatinib, imatinib), multikinase inhibitors (MKIs; e.g., sorafenib, sunitinib), monoclonal antibodies (mAbs; e.g., bevacizumab, trastuzumab), oral chemotherapy (e.g., capecitabine, hydroxyruea), hormonal therapy for treatment of breast or prostate cancer (e.g., aromatase inhibitors, gonadotropin-releasing hormones), and demethylating agents (e.g., decitabine, azacitidine). A total of 2,269 electronic medical records were screened; of these, 332 (6.8%) patients were eligible for the study. The primary reason for ineligibility was no TT use. A further 37 patients were excluded from data collection after selection for inclusion into the study due to no diagnosis of cancer or no use of TT. The final sample was N = 295 (Figure 1).

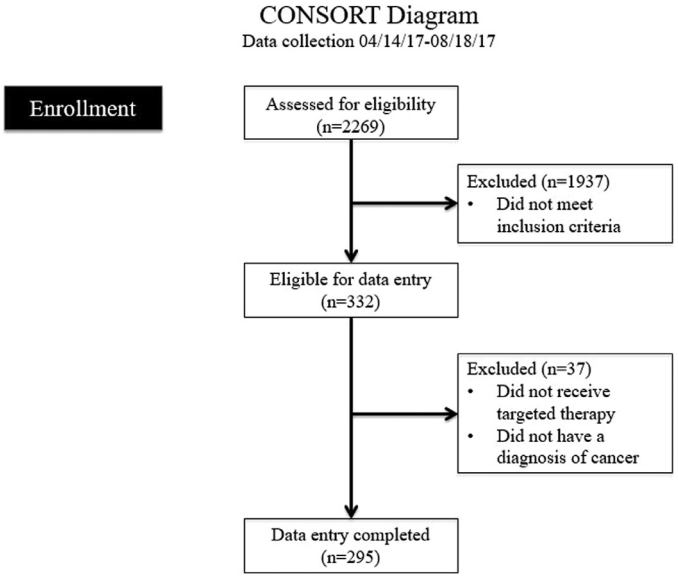

Fig. 1. A modified CONSORT diagram describes the screening and inclusion process of study participants.

Procedure and variables

For each patient, the visit date occurring before but closest to February 28, 2017 (date of IRB approval) was identified and labeled as the index date. All visits occurring in the one-year period prior to the index date were reviewed by the research assistants. For example, if a patient was last seen in June 2016, all visits between June 2015 and June 2016 were evaluated.

Descriptive variables included socio-demographic information (e.g., gender, race/ethnicity, occupation, health insurance, etc.), cancer type, stage of cancer, prior treatment of cancer, TT (e.g., start and stop dates, indication, dose reduction, etc.), and performance status recorded at the index date based on the Eastern Cooperative Group (ECOG) criteria, which ranges from 0 = fully active to 5 = dead.[29] Side effects of TT use that were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)[27] were extracted from the notes of the participant chart and documented in the study database. The NCI CTCAE is the most widely used grading scale in cancer clinical trials and provides an objective means for grading the severity of adverse events (1 = mild to 5 = death).

Data analysis

All statistical analyses were performed with IBM SPSS Statistics v.24.0 (Armonk, NY).

Descriptive statistics were computed for all variables to describe the data distributions and to characterize the study sample. Common side effects of TT were categorized by drug group (i.e. TKI, mAb, etc.), drug class (i.e., EGFR, anti-PDL-1, etc.), and the patient sample as a whole.

Results

All participants were over 85 years of age and over half of the participants were female (55.6%); 74.9% were white and 37.6% were widowed (Table 1). The majority of the patients had some type of health insurance (71.9%), and the most common type of health insurance was Medicare (62.4%). Less than half were prior smokers (41.4%) and close to half were never smokers (48.8%).

The types or sites of cancer varied greatly among the participants (Table 2), but the most common included breast (31.5%), prostate

Table 1
Participant characteristics of the study sample.

		Total sample (N = 295) *n* (%)
Gender	Male	131 (44.4%)
	Female	164 (55.6%)
Marital status	Married or partnered	99 (33.6%)
	Never married	16 (5.4%)
	Divorced	7 (2.4%)
	Widowed	111 (37.6%)
	Separated	1 (0.3%)
	Unknown	61 (20.7%)
Race	White	221 (74.9%)
	African American	66 (22.4%)
	Asian	5 (1.7%)
	Hispanic or Latino	1 (0.3%)
	Other	2 (0.6%)
Health care insurance?	Yes	212 (71.9%)
	No	79 (26.8%)
Type of health care insurance	Private	14 (4.7%)
	Medicare	184 (62.4%)
	Medicaid	2 (0.6%)
	Other	12 (4.1%)

Notes. TT = targeted therapy.

Table 2
Clinical characteristics of the study sample.

		Total sample (N = 295) *n* (%)
Currently smoking?	Yes	4 (1.4%)
	Never smoked	144 (48.8%)
	Prior smoker	122 (41.4%)
Cancer diagnosis	NSCLC	8 (2.7%)
	Colorectal	24 (8.1%)
	Breast	93 (31.5%)
	Prostate	61 (20.7%)
	GIST	8 (2.7%)
	Leukemia/dysplasia	53 (18%)
	Lymphoma	26 (8.8%)
	Other	22 (7.4%)
ECOG performance status	Fully active	56 (19%)
	Restricted but ambulatory	90 (30.5%)
	Up/about ≤50% of waking hours	28 (9.5%)
	Limited self-care	13 (4.4%)
	Disabled	2 (0.7%)
Mutational testing done?	Yes	146 (49.5%)
	No	59 (20%)
Mutational status	Wild type	20 (6.7%)
	Mutated	123 (41.7%)
Type of past cancer treatment	Surgery	96 (32.5%)
	Radiation therapy	53 (18%)
	Chemotherapy	40 (13.6%)
	Targeted therapy	4 (1.4%)
	None	57 (19.3%)
	Other	4 (1.4%)

Notes. TT = targeted therapy, NSCLC = Non-small cell lung cancer, GIST = Gastrointestinal stromal tumor, ECOG = Eastern Cooperative Oncology Group.

(20.7%), and leukemia or other dysplasia (18.0%). Generally, patients had a documented ECOG performance status of 0 (fully active; 19.0%) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 30.5%). Many patients underwent mutational testing as part of their cancer diagnosis work-up (49.5%), and 41.7% had an activating mutation in their tumor. Prior cancer treatments included surgery, radiation therapy, chemotherapy, and targeted therapy.

Just over one-third (37.6%; Fig. 2) of participants received oral hormonal therapy. Common types of TT included oral chemotherapy (13.2%), monoclonal antibodies (14.2%), injectable hormonal therapy (11.9%), and tyrosine kinase inhibitors (13.2%). Of the 295 participants, 1.0% were reported to have no side effects of TT at all, 25.8% were reported to have "tolerated well" their TT, and 28.5% of the patients had side effects related to TT use recorded in their electronic medical record (n = 84). For patients who had side effects related to TT use documented in their chart, over 100 individual side effects were reported. Fig. 3 depicts the most common side effects documented in the medical chart.

Discussion

The purpose of the study was to expand on what is currently known about TT use in older adults by conducting a retrospective chart review of older adults with cancer who were treated in the Baltimore area over the last seven years. An expected number of older patients treated with a wide range of TTs and with a similar number of side effects as seen in younger individuals was found during the study analysis. For the most part, the sociodemographic and clinical characteristics of the patient sample were representative of the general cancer population.[30]

The patients in the study took a wide range of TT; however, most published research of TT use in older adults has focused on imatinib mesylate, a TKI approved for treatment of CML in the chronic phase. Overall, initial results for studies examining effectiveness of imatinib

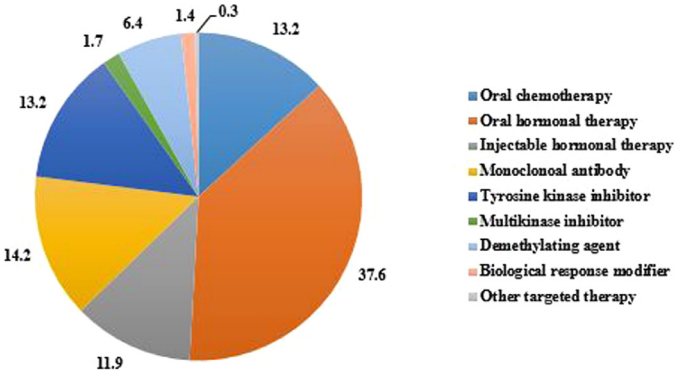

Fig. 2. The most commonly recorded types of targeted therapy in the patient sample (% of *N* = 295).

mesylate did not vary by race/ethnicity, socioeconomic status, geographic residence, or insurance status, even after being adjusted for age at diagnosis.[28] Bjorkholm and colleagues[19] examined relative survival for Swedish patients with CML in five age groups across five time periods over 36 years. They found the time period with the greatest improvement in relative survival was from 2001 – 2008 (imatinib mesylate was approved in Sweden in 2001) and the age group with the best improvement included patients up to 79 years of age; however, the authors noted that most patients older than 80 years of age took hydroxyurea as first-line therapy, and only 18% were treated with imatinib mesylate. It is unclear whether this was due to potential TT toxicity or to other reasons. Patient side effects were not reported. In a sub-analysis of a Phase II study examining nilotinib,[31] a second-generation TKI for treatment of CML, 8% of the patient sample was older than 80 years, and overall survival and frequency of side effects were similar between older and younger adults on the trial. In contrast, overall survival has been shown to be negatively impacted by higher age in patients taking azacitidine for treatment of acute myeloid leukemia.[32]

The side effects related to TT use that were recorded in the EMR were consistent with commonly reported side effects of the therapies the patients received (e.g., hot flashes with aromatase inhibitors, rash and/or diarrhea for TKIs inhibiting the epidermal growth factor receptor).[31,32] The intent of the present study was to collect data with regard to frequency, duration, and reasons for discontinuation of TT; however, information about participant level of education completed, cancer subtype, disease stage, NCI CTCAE grade, reason for discontinuation of TT, reason for interruption of TT, and reason for dose reduction of TT was not reported in more than 50% of the charts that were reviewed. It is unclear whether this was unique to the hospital system, but the findings suggest that future research is needed to examine effective strategies for collecting

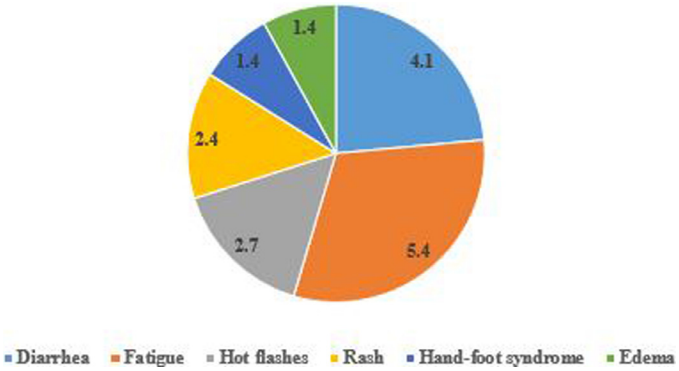

Fig. 3. The most commonly recorded symptoms in the patient sample (% of *N* = 98).

symptom information and/or system or process improvements for documenting such information.

Study limitations

The research findings should be interpreted with several limitations in mind. First, the study was retrospective and was limited to the data already collected and stored in the medical records. There was a large amount of missing data related to duration of TT use and reason for interruption, reduction, or discontinuation of TT; therefore, the third aim of the study was not addressed. A very broad definition of TT was used and included different classes of cancer therapies, including oral hormonal therapy, monoclonal antibodies, and others. Further, the indications for use and side effect profiles vary greatly among these patients. Given this, future research that examines the impact of TT use on patients ≥85 years of age should focus on one type of TT or include a larger sample size for each type of treatment.

Conclusions

The purpose of this study was to describe TT use in patients with cancer ≥85 years of age. Patients in this age group in this study were prescribed TT for treatment of cancer, but reasons for dose reductions, interruptions, and/or discontinuations as well as symptoms related to TT were inconsistently documented in the electronic medical chart. Reported side effects related to TT use were consistent with what is currently known about the individual medications that the patients received as treatment for their cancer. Given the wide range of TT found in the patient sample and the different classes of TTs and indications for use, it is difficult to analyze, interpret, and translate research findings of the impact of TT patients ≥85 years of age. As such, there is a need for prospective studies to examine TT use in patients of extreme age with regard to health- related quality of life, functional status, adherence to medication, and symptom burden and to identify individuals at risk of discontinuing TT due to side effects or poor quality of life.

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