EDITORIAL

To Treat or Not to Treat

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Editorial for article by Sineshaw et al., Treatment Patterns Among De-novo Metastatic Cancer Patients Who Died Within One Month of Diagnosis
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Despite considerable advances in novel cancer therapeutics over the past few decades, patients diagnosed with metastatic cancer are still highly likely to die of their disease. The decision regarding whether to treat, or not to treat, an individual patient depends on many factors, including tumor biology, disease burden, comorbidities, patient preferences, cost, as well as likelihood of benefit and toxicity from treatment. These decisions are even more complex when patients present de novo with very advanced disease due to concerns about being either too nihilistic or overly aggressive and potentially prohibiting the provision of quality palliative care before death (1). Evaluation of quality of care in this context is challenging, and there is a paucity of evidence in the literature to guide clinical practice.

In recognition of the need for a more balanced care approach for cancer patients, the American Society of Clinical Oncology as well as other professional international organizations have advocated that "combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden" (2). However, for the most part, oncological and palliative care services and cultures remain quite disparate, with the oncologist focused on providing treatment to retard or cure the cancer, whereas palliative care focuses on the symptoms and existential concerns of the patient. Increased efforts to systematically integrate both streams of care are in action and will continue to be adapted to suit different institutional infrastructures and cultures (3).

In the article accompanying this editorial, Sineshaw et al. undertook a detailed analysis of the treatment patterns of patients who died within 1 month of diagnosis of stage IV cancer (4). This was based on a large retrospective dataset from the American National Cancer Data Base between 2004 and 2014. The authors are to be commended on their systematic approach to addressing this important and complex issue and for spearheading efforts to identify factors involved in treatment decision-making in patients with rapidly progressive de novo metastatic cancers.

Sineshaw et al. reassuringly affirmed that the majority (73%) of this patient group did not receive any cancer-directed treatment, and there were declining trends for most modalities including surgery, chemotherapy, and radiation therapy by cancer type over the study period (4). Patients with coexistent clinical risk factors such as increased age and higher comorbidity score were less likely to receive treatment, as were patients from a lower socioeconomic background or racial minorities. For instance, the authors found that uninsured patients had lower odds of having surgery, radiotherapy, or chemotherapy compared with their privately insured counterparts. Of note, patterns of treatment varied depending on the type of treatment center.

These are very interesting findings, reflecting both potentially appropriate and inappropriate decision processes, as discussed by the authors (4). On the one hand, the fact that most patients did not receive any surgery, radiation, or chemotherapy near end of life may be a reflection of better awareness of disease trajectory and patient prognosis, leading to care focusing on quality of life and supportive measures. However, differences in treatment associated with factors such as socioeconomic status, ethnicity, and type of treating facility raise concerns of inequity of care. A retrospective database review is clearly not able to determine all the factors involved in individual patient decision-making, nor balance their relative importance for each individual patient. However, the information provided by this study does underscore the fact that patients with advanced and imminently fatal cancer are a unique and complex population requiring specific consideration in future research exploring decision-making in patients with advanced cancer.

This patient group has generally not been included in clinical trials assessing treatment efficacy and toxicity, so extrapolating data for the purpose of counseling patients and treatment decision-making is prone to potential inaccuracy. We need "real life" data on responses and toxicity in this setting to balance potential treatment benefits and costs and to counsel

our patients. As noted by Sineshaw et al., their dataset was specifically limited to patients who died within 1 month of diagnosis of advanced cancer (4). Without knowing the total number of patients diagnosed with potentially imminently fatal disease over the time frame, including those who did not die within a month, we cannot comment on the efficacy of the various treatments or the appropriateness of the treatment decisions. If a high proportion of all patients treated died within a month, then the treatment could be considered futile. Conversely, if the proportion is low, then receipt of such treatment may indeed be very reasonable, even if it was ultimately unhelpful for an individual patient.

Furthermore, to initiate active treatment within 1 month of death does not necessarily imply futility. The appropriateness of treatment decisions near end of life should also be considered in the context of intent and tumor biology. Many treatments may be explicitly intended to improve symptoms, rather than to prolong duration of life, for example, surgery to perform a diverting stoma, stenting to relieve a bowel obstruction, or radiotherapy to relieve bone pain or bleeding from a tumor. These measures offer palliative benefits that would generally be considered worthwhile by patients and their clinicians even if they are not expected to prolong life. The risk however lies in the potential for such measures to add toxicity without achieving their palliative goal, hence potentially worsening patients' quality of life. Chemotherapy administered in the last month of life is unlikely to achieve a palliative benefit in general. However, chemotherapy for exquisitely chemo-sensitive tumors such as small-cell lung cancer and targeted therapies for HER2-positive breast cancer or lung cancer with EGFR mutations or ALK rearrangements may temporize the disease and so may reasonably be offered in the context of very advanced disease. Of note, the emerging role of novel therapeutics including immunotherapeutic agents and gene therapy will introduce another layer of complexity to treatment decision-making and deserves further consideration. Sineshaw et al. have appropriately acknowledged the lack of specific information regarding treatment intent as one of the limitations of this dataset (4).

We need better measures of the efficacy of palliative interventions, particularly in the setting of patients approaching end of life. Although anecdotally this often appears to be the case, determining if these measures are futile or not in patients approaching the end of life requires prospective assessment of symptoms and patient reported outcomes. There are real challenges in performing this type of research as patients approach end of life due to the clinically unstable and emotionally charged situation. Random assignment is generally not appropriate, and patients may not be well enough or stable enough to answer detailed patient reported outcomes questionnaires. Possible alternative methods might include involving a caregiver or possibly nursing staff in assessments (5).

We also need better tools to improve our ability to prognosticate. The major impediment to optimal treatment decision-making lies in the difficulty with accurately prognosticating patients' disease trajectory despite current knowledge of cancer biology. Doctors are notoriously poor at predicting life expectancy in patients with advanced malignancy, particularly when prognosis is guarded (<3 months) (6, 7), and this hinders our ability to appropriately select who to treat, or not to treat. This study suggests that we might be improving in our selection process, given the decreasing number of patients over time receiving treatment in their final weeks of life. Nonetheless, there is clearly room for improvement. Defining therapy goals in light of uncertainty towards the immediate future can be confronting for all parties involved including clinicians, patients, and caregivers. Early communication, wherever possible, would help establish mutual understanding and allow resources to be directed toward what patients deem to be an acceptable quality of life, particularly when death is imminent.

Notes

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