Health-related quality of life in sarcoma patients: *enhancing personalized medicine.*

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We read with great interest the Special Series entitled 'Novel Therapeutic and Diagnostic Advances in Bone and Soft Tissue Sarcomas.' These articles provide a comprehensive insight into current knowledge and evolving research in this heterogeneous group of tumors. Although relevant diagnostic and therapeutic aspects of patient care are considered, there is almost no reference to the patient perspective of these advances. Most authors acknowledge the need for individualized care, with respect to clinical, genetic and molecular factors, however only Gounder et *al* refer to health-related quality of life (HRQoL) measures as potentially meaningful clinical endpoints in locally advanced connective tissue tumors.

Historically, evaluation of oncological treatments has focused on objective outcomes such as radiological response, progression-free and overall survival, and healthcare-provider perspective of treatment-related toxicities. More recently, increasing attention has been given to patient reported outcomes (PROs), defined as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else,' in order to evaluate treatment efficacy(www.fda.gov). PROs include a range of outcomes such as

symptoms, functioning and HRQoL. HRQoL is the most widely used PRO and is a multidimensional concept that includes the patient's perception of the impact of the disease and its treatment on physical, psychological and social functioning.[1] Incorporating PROs into clinical practice can facilitate communication, improve symptom control and patient satisfaction and reduce hospital admissions.[2] A recent study in patients with metastatic solid tumors showed that routine PRO monitoring and immediate response to adverse events led to a five month survival benefit compared with standard care[3]: more than most new drugs for metastatic cancers approved by the FDA in 2016(www.fda.gov).

Data on HRQoL in sarcoma patients are limited, however many patients experience a substantial burden of physical and psychological symptoms, with an adverse impact on HRQoL.[4] Integration of HRQoL with traditional measures of therapeutic response will provide a more comprehensive assessment of the efficacy and toxicity of novel therapies for sarcoma patients.[5] Symptomatic toxicities are frequently underreported by clinicians, therefore PROs are a vital component of symptom detection, monitoring and early intervention.[6] Precise assessments of how patients feel and function offer important additional information to evaluate the risks and benefits of treatments.[1] Patient experience is a key aspect of drug development, and survival alone is inadequate to determine net clinical benefit.[7] Although some novel treatments have been approved for sarcomas over the last few decades, detailed data on short- and long-term side-effects and HRQoL are scarce.[4] The PALETTE study of pazopanib versus placebo, as second-line or greater treatment for advanced soft tissue sarcomas, is one of the few sarcoma trials which reported HRQoL as an exploratory endpoint.[8] Pazopanib improved progression-free survival without relevant deterioration in HRQoL compared with

placebo.[8] This demonstrates that combining HRQoL with clinical data can show overall clinical treatment benefit.

One of the biggest challenges in sarcoma is how to assess HRQoL in this heterogeneous patient group. Previous studies have predominately used generic HRQoL instruments (EORTC-QLQ-C30, SF36, FACT-G), however these tools do not efficiently capture the unique experiences of sarcoma patients (e.g. disease-localization, treatment-specific symptoms) and thus lack content validity. Traditionally inadequate content coverage has been addressed using a tumor-specific questionnaire that captures all disease-specific HRQoL issues, in conjunction with generic HRQoL measures. Given the heterogeneity of sarcomas including patient age, histological subtype, physiological locations, disease stage and rapidly changing treatment landscape, associated with variable mechanisms of action and toxicity profiles, it may be challenging to develop one sarcoma-specific questionnaire that meets the needs of clinical practice, academia, and industry. Standardized, so called "static" questionnaires consisting of a fixed set of items may not be relevant for every sarcoma patient and may miss important patient-reported adverse events. Consequently, a more flexible approach is needed to assess the impact of treatments, provide optimal supportive care and ultimately translate into meaningful outcomes for sarcoma patients.[9] One option is to combine standardized PRO questionnaires with validated items from item libraries (e.g. PROMIS, EORTC), to ensure adequate assessment of specific treatments and their effects on common health problems.[9]

In this era of personalized medicine, the principal focus has been on clinical and tumor characteristics without addressing individual patient perspective. If we really want to make a difference, truly provide personalized care and run trials that are attractive to

patients, we should routinely involve patients in trial design and integrate HRQoL assessments into clinical practice and research.[10] This will enable provision of a more holistic approach to the overall management of patients.

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