**Personalized Oncology Therapies Require Personalized Oncology Patient-Reported Outcome Measures**

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**KEY POINTS**

The treatment paradigm in oncology has shifted, moving from conventional chemotherapies to personalized medicine, including immunotherapies.

Personalized medicine leads to individual-specific risks and benefits; thus patient-reported outcomes also need to be personalized to capture the relevant and appropriate concepts that matter to patients.

Qualitative interviews with patients to collect their experience within an oncology trial: an innovative approach to document patient-perceived treatment benefit.

**Tumor size, overall survival, progression-free survival, treatment side effects, disease symptoms**—these are all central clinical features to document in oncology clinical trials. While most features are assessed using imaging or biological samples, one should not forget the patient’s voice to give a meaning to the observed changes on how a patient feels and functions. Only a patient can explain how a tumor shrinking by half its size actually benefits his daily life; only a patient can report how debilitating peripheral neuropathy can be; only a patient can report on how her pain or bowel movements have been affected by her treatment. The addition of the patient voice into the interpretation of the efficacy and safety data shall contribute to the assessment of the value of the treatment.

Collecting patient-reported outcomes (PRO) data has become a must in clinical research. Basch et al provided a comprehensive set of information on the selection, implementation, data analysis, and reporting of PRO in oncology trials [6]. PRO data are highly valued by major stakeholders, including payers and regulators. The European Medicines Agency (EMA) dedicated a specific appendix to PRO assessment in its guideline on the evaluation of anticancer medicinal products in man that came into effect as of November 2016. The US Food and Drug Administration (FDA) also refers to the use of PRO in particular to assess tumor symptoms and treatment-related toxicity in its 2007 guidance for industry on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. The Agency is particularly interested in distinguishing through separate assessments, the treatment-related side effects, disease-related symptoms, and physical functioning [3]. More recently, the FDA confirmed its interest in having sponsors incorporating the patient perspective in oncology trials, in particular to inform safety profiles of the new cancer drugs under development [4].

The concomitant increase in the documentation of patient’s perspective in oncology trials has been reported in the review by Zagadaïlov et al. Between 2006 and 2012 for about 85% of clinical oncology trials, sponsors disclosed on ClinicalTrials.gov the inclusion of a PRO to address an endpoint evaluating health-related quality of life and/or symptoms. In contrast, between 2002 and 2006 this percentage was down to 12% [5]. Cancer is by itself a group of myriad diseases with specificities and multiple treatment approaches, making it a challenging field for PRO assessments.

Today, relatively few PRO questionnaires are used in oncology. The European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QLQ) questionnaires and the Functional Assessment of Cancer (FACT) questionnaires have become standard instruments used in many trials for many types of cancer, including common cancers such as lung and breast cancers [6,7] as well as rarer cancers such as head and neck [8]. Their structures are very close, with a core module to which a specific cancer type module can be added. Their content is also quite similar, covering not only health-related quality of life, including physical functioning, but also treatment-related side effects and disease-related symptoms.

**...in the evolving era of cancer care, both a conservative approach with a legacy questionnaire and an innovative approach with specific questionnaires and qualitative interviews should be undertaken in immuno-oncology trials for the collection of patient-reported outcomes data**

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A shift in treatment paradigm in oncology has occurred, leaving conventional chemotherapies and moving toward personalized medicine, with first the development of tumor-targeted therapies and more recently the development of immunotherapies such as the blocking antibodies to cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) [9]. With better efficacy and milder toxicity profiles of immunotherapy agents, the question around risk-benefit ratio has become less relevant, while the cost-effectiveness ratio and more particularly, the cost-utility ratio for such therapies have become a primary interest for health technology assessment bodies and payers.

There are limitations in the use of currently available questionnaires, in particular in light of the value-based healthcare, and authorities’ requirements to use questionnaires for the purpose and context of use. These questionnaires have been designed for use in cancer patients with a range of disease stages and undergoing different treatments. Typically, these questionnaires have been developed initially to address the ethical question about the risk-benefit ratio of cytotoxic therapies. The frequency of administration of PROs was adapted to the treatment cycles. Thus, despite the fact that these questionnaires are validated and well-developed following standard methodology, they may become progressively outdated with the implementation of personalized medicine. Still, one should not totally move away from the standard questionnaires. While the shift in treatment paradigm is not completed, trials comparing conventional chemotherapies to immunotherapies would benefit from the use of the standard questionnaires to demonstrate patient-perceived treatment benefit of the new treatment in contrast to the former standard therapies.

For immunotherapies, the dose, treatment duration, and follow-up care are all patient-dependent parameters. Consequently, PRO also needs to be personalized to capture the relevant and appropriate concepts that matter to patients. In that sense, efforts are made by developing item banks to create customized questionnaires. This is the case of the EORTC item library, and also the National Institutes of Health-funded Patient-Reported Outcomes Measurement Information System (PROMIS®) and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™).

Still, there are several challenges in immuno-oncology trials. First, it is clear that there is a need to define specific hypotheses and use specific appropriate measures to monitor separately health-related quality of life, treatment-related side effects and disease-related symptoms. Very limited information is available in the literature to identify the concepts of interest to cancer patients receiving immunotherapies. Pre-established conceptual frameworks to support the relevance of a concept or another is missing it, making it a challenge to define the right specific hypothesis and to choose the right PRO instrument that would document meaningful treatment benefits. A second challenge for the administration of PRO instruments resides in the sample size. Indeed, only patients with a specific genetic or epigenetic profile are eligible for specific immunotherapies. A third challenge in oncology trials is linked to cancers for which there are no currently available standard treatments. Such trials have frequently open-label, single-arm designs. In that context of multiple challenges, qualitative interviews with patients to collect their experiences with the study treatment within the trial may bring solutions to inform patient-perceived treatment benefit. Ideally, qualitative interviews should be integrated already in the first version of a study protocol from the start to maximize their added value to the trial. O’Cathain et al. described various contributions of qualitative research in clinical trials. It goes from the situation where the qualitative research is a stand-alone feature taking the advantage of accessing patients through the trial to the situation where the qualitative research is more than just complementary but informative and essential to the interpretation of the outcomes of the trial [10]. Integrating interviews at several time points of the trial to allow a longitudinal analysis should help capture changes over time linked to the study treatment as reported by the patients [11]. This approach requires on one hand the qualitative analysis to be performed continuously along the trial and on the other hand to develop continuously personalized follow-up interview guides to properly track the evolution of the concepts raised by an individual patient. While this could be cost- and time-consuming, this approach of repeated interviews within a trial limits the memory bias that could be an issue with exit interviews in lengthy oncology trials.

In conclusion, in the evolving era of cancer care, both a conservative approach with a legacy questionnaire and an innovative approach with specific questionnaires and qualitative interviews should be undertaken in immuno-oncology trials for the collection of PRO data. One should rely on the use of a standard legacy questionnaire to benchmark and compare to existing data. But, one should also use a specific outcome questionnaire for a specific hypothesis testing that could support a PRO claim in a drug label. Qualitative interviews should be implemented further to provide an explanation and understanding of the study treatment efficacy and safety, to guide the interpretation of the quantitative PRO and clinical data, and last but not least, to capture the individual features of personalized medicine. What indicates a statistically significant 10-point improvement on a 100-point scale assessing fatigue? Only patients can tell how it translates practically; it may not actually change anything in the patients’ lives, but it could also lead to significant changes if they can visit their friends, go shopping, or prepare a meal without a required aid. This suggestion of adding

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qualitative interviews fully aligns with the FDA public workshop that was held on December 18, 2017 on the collection and submission of patient experience data to inform medical product development and regulatory decision making.

REFERENCES

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