What role does the patient perspective play in determining access to innovative therapies?

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Introduction

- New oncology drugs are evaluated first by regulators, then by payers and clinicians, all of whom are key stakeholders determining access to treatment.
- The 21st Century Cures Act 2016 requires the US Food and Drug Administration (FDA) to do more to incorporate patient perspectives into their decision-making, particularly patients' experience of disease and effects related to treatment.[1]
- A quantitative approach to understanding patients' treatment experiences is the use of patient-reported outcome measures (PROMs). Patients are at the center of PROM development, and these instruments are used to capture information directly from the patient, with the aim of quantifying changes in feelings and functioning.
- However, there is much debate about the reliability of PROMs and the consistency in their use.
  - Although the American Society of Clinical Oncology (ASCO) value framework awards bonus points for therapies that improve quality of life (QoL), the authors acknowledge that PROMs are not included in the framework and state that "much work is needed to develop reliable assessments and consistent use of PROs".[2]
  - Similarly, the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) approach to recognizing QoL benefits is still evolving, and has been deferred for consultation with patient representative organisations.[3]
- Even though PROMs are widely used in clinical trials, only four have been "qualified" by the FDA and only one of these is for use in oncology (the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire, NSCLC-SAQ).[4]
- The FDA does not require an instrument to be qualified for it to be used in a clinical trial.[5] FDA guidance on the use of PROMs includes definitions of QoL and health-related QoL (HRQoL), but the agency considers QoL to be too general and undefined to be appropriate for a medical product claim:[6]
  - QoL: "A general concept that implies an evaluation of the effect of all aspects of life on general well-being"
  - HRQoL: "A multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life".
- While the European Medicines Agency (EMA) takes a holistic view of the effects of treatment on a patient's life,[7,8] which may include anxiety, depression, and financial issues, FDA assessments of oncology drugs remain focused on symptoms (e.g., adverse events [AEs] such as nausea and vomiting).[9]
- We sought to establish how patient-relevant outcomes beyond survival were considered in evaluations of oncology drugs by regulators, oncology societies, and payers/health technology assessment [HTA] agencies, and how this might change in future.

Methods

- The following sources were reviewed for reference to PROMs, QoL, or patient-reported disease symptoms (other than standard AE information):
  - EMA summaries of product characteristics (SPCs) and FDA package inserts from oncology products first approved in 2017 (product approvals were identified using online sources[10–12])
  - EMA Committee for Medicinal Products for Human Use (CHMP) meeting highlights (2017 meetings)[12]
  - Documents from completed or ongoing assessments of the products identified (published up to 16 May 2018) by national HTA agencies in England (National Institute for Health and Care Excellence, NICE), France (Transparency Commission, TC), and Germany (Federal Joint Committee [Gemeinsamer Bundesausschuss], G-BA)
  - Clinical trial registry information (from clinicaltrials.gov) for Phase 2 or 3 industry-sponsored interventional trials for advanced cancer initiated between January 2013 and 30 April 2018.
- Product line extensions and generics/biosimilars were excluded from the analysis of regulatory documents and HTA decisions.

Results

Review of regulatory labels

- None of the 16 products approved by FDA in 2017 had references to PROMs or patient-reported symptom measures (other than AEs) in the package inserts.
- Of the 13 products approved in Europe, 7 reported PROMs or symptom measures in the SPC (Table 1).

Table 1 PROMs or patient-reported symptom measures in EMA summaries of product characteristics (products approved in 2017)

Product	Indication (brief description)	PROM or other relevant information
Alectinib	Adults with ALK-positive advanced NSCLC	
Atezolizumab	Second-line treatment of locally advanced or metastatic urothelial carcinoma or NSCLC	EORTC QLQ-LC13; prolonged time to deterioration of chest pain (vs docetaxel) but deterioration in other symptoms similar between group; results should be interpreted with caution due to open-label study design
Avelumab	Merkel cell carcinoma	
Dinutuximab beta	High-risk relapsed/refractory neuroblastoma	
Inotuzumab ozogamicin	Relapsed or refractory B-cell precursor acute lymphoblastic leukemia	EORTC QLQ-C30, EQ-5D, EQ-VAS; most scores favored inotuzumab ozogamicin (vs chemotherapy)
Lutetium Lu 177 dotatate	Somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors in adults	QoL listed as a secondary endpoint (no specific measure or data reported)
Mechloroethamine hydrochloride	Topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma	
Midostaurin	FLT3 positive acute myeloid leukemia, mastocytosis, mast cell leukemia	
Niraparib	Relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.	FOSI, EQ-5D; data indicated no difference in QoL in for niraparib vs placebo
Padeliporfin	Low-risk prostate cancer	IPSS (general increase in scores until month 24 after VTP procedure); IIEF-15 (initial decrease in scores at day 7 after VTP, followed by improved scores up to month 24)
Ribociclib	Breast cancer (HR+, HER2-, advanced/metastatic)	Global health status/QoL (no specific measure reported); no relevant difference (ribociclib plus letrozole vs placebo plus letrozole)
Telotristat ethyl	Carcinoid syndrome diarrhea	Patient exit interview sub-study; patients were asked to characterize the degree of change experienced during the trial; more patients on telotristat ethyl (vs placebo) reported being "very satisfied"
Tivozanib	Advanced renal cell carcinoma	

Gray cells indicate that no relevant information was reported in the summary of product characteristics.

ALK, anaplastic lymphoma kinase; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; EORTC QLQ-LC13, EORTC Quality of Life-Lung Cancer; EQ-5D, EuroQol 5-Dimension questionnaire; EQ-VAS, EuroQol Visual Analogue Scale; FLT3, Fms-related tyrosine kinase 3; FOSI, Functional Assessment of Cancer Therapy-Ovarian Symptom Index; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; IIEF-15, International Index of Erectile Function; IPSS, International Prostate Symptoms Score; NSCLC, non-small cell lung cancer; PROM, patient-reported outcome measure; QoL, quality of life; VTP, Vascular-Targeted Photodynamic therapy.

- A review of CHMP meeting highlights found that a failure to show improvement in QoL was cited among reasons for issuing a negative recommendation for supportive care products such as:
  - Anamorelin hydrochloride, intended for the treatment of anorexia, including unintended weight loss in NSCLC
  - Human immunoglobulin G1 monoclonal antibody specific for human interleukin-1 alpha, intended for treating debilitating symptoms of advanced colorectal cancer.

Review of HTAs

- Of the 13 drugs approved in Europe in 2017, NICE (England) had published decisions on five, the TC (France) on five, and the G-BA (Germany) on eight.
- For NICE, all assessments or associated committee papers referred to PROMs and/or QoL.
  - A lack of significant difference in PROMs was noted for most products although trends in improvements in some domains, or time to deterioration were noted in the committee papers for avelumab, atezolizumab (in NSCLC), inotuzumab, and ribociclib.
  - For all assessments, health state utility values were used in the economic models in order to calculate the cost per quality adjusted life year. For some products, utility decrements were applied to account for AEs.
- While three of the products assessed by the TC included PROMs in the trials, none of the products were considered to deliver any improvement in QoL.
  - No conclusions could be drawn in open-label trials (alectinib and inotuzumab); for ribociclib, an exploratory analysis suggested no difference in QoL between treatment groups.
  - A lack of QoL data was noted in the reports for dinituximab beta and mechloroethamine hydrochloride.
- All resolutions by the G-BA referred to PROMs and/or QoL.
  - Symptom improvements were noted for some products (e.g., alectinib and atezolizumab) but there was no improvement in functioning.
- It is unclear whether PROM data influenced the decisions in England and France, but according to German legislation (article 5, paragraph 7 Verfahrensordnung) they are a contributing factor in determining the level of benefit.

Review of clinical trial registry information

- A total of 796 oncology trials were retrieved through the search; after excluding Phase 1/Phase 2 trials, 514 trials records were reviewed.
- The proportion of clinical trials reporting the use of a PROM increased from 22% in 2013 to 30% in 2018 (to 30 April; Figure 1). A higher proportion of Phase 3 than Phase 2 trials included PROMs.
- A considerable range of PROMs was used in the trials (Figure 2).
  - The most commonly used PROMs (EORTC QLQ-C30 and EQ-5D) were included in 39% and 20% of the trials, respectively. The EORTC QLQ-C30 was often used in conjunction with a module specific to the particular cancer.

Figure 1 Use of PROMs in Phase 2 or 3 industry-sponsored interventional trials for advanced cancer (trials initiated between January 2013 and April 2018)

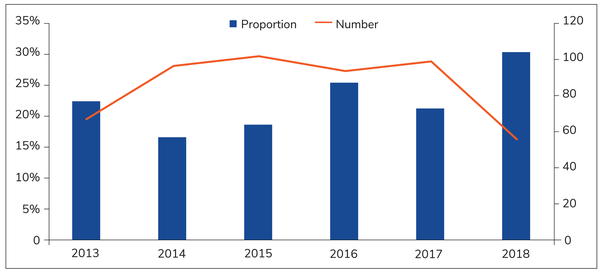

Figure shows the proportion of trials including a PROM (bars) and the total number of trials initiated each year (line). The total number of trials appears to decrease in 2018 but the data are for January to April only. PROM, patient-reported outcome measure.

Figure 2 Most commonly-used PROMs in Phase 2 or 3 industry-sponsored interventional trials for advanced cancer (initiated between January 2013 and April 2018)

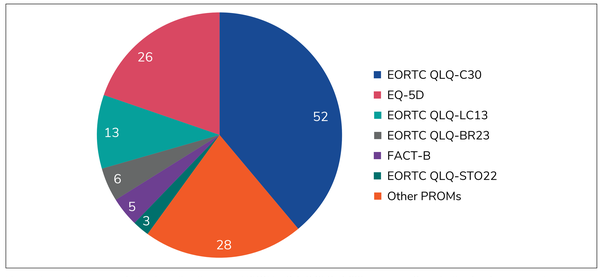

Figure shows the number of trials including the named PROM. EORTC QLQ-BR23, European Organisation for Research and Treatment of Cancer Quality of Life-Breast Cancer; EORTC QLQ-C30, EORTC Quality of Life Core Questionnaire; EORTC QLQ-LC13, EORTC Quality of Life-Lung Cancer; EORTC QLQ-STO22, EORTC Quality of Life-Gastric Cancer; EQ-5D, EuroQol 5-Dimension (3 Level or 5 Level); FACT-B, Functional Assessment of Cancer Therapy-Breast; PROM, patient-reported outcome measure.

Discussion

- Our review found no mention of PROMs in FDA package inserts for products approved in 2017, in contrast to an earlier assessment;[13] this may reflect a recent decline in PROM labeling for new drugs across all therapy areas.[14]
- Several European SPCs and HTAs mention PROMs, but their impact on decision-making is not clear.
- The inclusion of PROMs in clinical trials appears to be increasing overall, from 22% of trials initiated in 2013 to 30% of those initiated in 2018 (January to April).
- The role of PROMs is important to regulatory agencies in their assessment of risk:benefit, but PROM evidence also provides strong support of the value of products to payers. European payers in particular expect to see PRO data for oncology products as they want to understand not only the quantity of life offered by a product, but also the quality. However, although QoL is a criterion within ASCO and ESMO value frameworks, the role of PROMs as evidence of a product improving or delaying decline in QoL is not clear.
- Although the focus of our work was on regulators and payers, it is important to recognize the value of PROM data for clinicians and ultimately patients; effects on QoL may be more important to the patient than to any other stakeholder[15] and may help in selecting the most appropriate treatment.
- Patients should be involved in any discussion regarding what is relevant or meaningful to them.

Limitations and future work

- For regulatory approvals, we only reviewed package inserts or SPCs (full regulatory assessment reports were not reviewed); it is possible that PROMs were considered as part of the evaluation but were not included in the label.
- PROMs are only one factor considered as part of a product evaluation and it is difficult to identify the extent of their influence in stakeholder decision-making.
- Future reviews could include:
  - Examining whether PROMs included in trials reported here are ultimately included in subsequent regulatory and payer assessments
  - Monitoring the qualification of PROMs by the FDA, the inclusion of these instruments in trials, and whether they translate into label claims
  - Exploring the variation of PROMs used in clinical trials for different types of cancer.

Conclusion

- To date, the 21st Century Cures Act appears to have had no impact on the inclusion of PROM data in FDA package inserts; however, the use of PROMs in clinical trials appears to be increasing, which could reflect the influence of the FDA on trial design.
- PROMs appear to have had wider consideration in Europe.
- The use of PROMs and other patient-relevant measures of benefit by stakeholders determining access to innovative therapies should be monitored and encouraged further.

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