Revisiting Expectations in an Era of Precision Oncology

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Abstract

As we enter an era of precision medicine and targeted therapies in the treatment of metastatic cancer, we face new challenges for both patients and providers alike as we establish clear guidelines, regulations, and strategies for implementation. At the crux of this challenge is the fact that patients with advanced cancer may have disproportionate expectations of personal benefit when participating in clinical trials designed to generate generalizable knowledge. Patient and physician goals of treatment may not align, and reconciliation of their disparate perceptions must be addressed. However, it is particularly challenging to manage a patient's expectations when the goal of precision medicine – personalized response – exacerbates our inability to predict outcomes for any individual patient. The precision medicine informed consent process must therefore directly address this issue. We are challenged to honestly, clearly, and compassionately engage a patient population in an informed consent process that is responsive to their vulnerability, as well as ever-evolving indications and evidence. This era requires a continual reassessment of expectations and goals from both sides of the bed.

Introduction

As we enter an era of precision oncology, genomic characterization is playing an increasingly larger role in individualized treatment.[1-3] However, precision oncology research challenges existing research guidelines and regulations. The very nature of such "basket" or "registration" trials defies current norms of standardization. Despite overwhelming enthusiasm, few enrolled patients have benefitted from involvement in these early efforts.[4]

A multi-disciplinary approach is necessary to convey to prospective subjects the complexity involved in participating in a precision medicine trial. Participants in clinical trials are often challenged by misapprehensions that the purpose of clinical research is to gain generalizable knowledge regardless of whether the individual will benefit from the intervention of the trial.[5] With the rapid growth of an exciting field comes new challenges for patients and providers alike in considering this concept.

Contextualizing Goals

Patients with advanced cancer have disproportionate expectations of the probability of personal benefit when consenting to new therapies, such as precision oncology. This disconnect may influence their decision. Weeks *et al* showed the majority of patients with stage IV lung and colon cancer did not recognize that their treatment regimen was unlikely to lead to a cure.[6] This alarming result calls into question the effectiveness of our informed consent process, as well as our patients' intense vulnerability and potentially misplaced optimism.[7]

This complex area of informed consent is magnified in precision oncology trials in which neither outcomes nor toxicities are well-characterized. The individualized nature of precision medicine protocols, in which treatment is driven by personalized data interpretation, is more evocative of traditional clinical care—confounding careful delineation of the clinical and

research spheres. At this intersection, the distinction between a "patient" and a "subject" becomes obscured. Thus, we must not only ensure that our current patients are fully informed about their personal therapeutic options but also reconcile our desire to obtain data integral to advancing cancer therapeutics for future patients.

Clinicians must be cognizant of patients' goals of care when discussing precision oncology trials. For patients, the goals that motivate enrollment in a precision oncology trial may include extending life, reducing symptoms, avoiding toxicities associated with therapy, or cure. Patients may also recognize an intrinsic altruistic motivation, but this is often secondary to the hope for personal benefit.[8] This dichotomy is present in all clinical research, but the uniquely personalized nature of precision trials coupled with the vulnerability of subjects with few therapeutic options make this more difficult to reconcile. There is currently a dearth of data exploring these themes in precision oncology, although empiric studies are ongoing.[9] In response, the National Cancer Institute has elicited information regarding gaps, opportunities, collaborations and areas of outreach in bioethics and cancer research.[10]

As providers, we must reconcile and make explicit to patients our goals to obtain data integral to advancing cancer therapeutics for future patients, with the personal impact current patients experience. Currently, the majority of precision trials remain are early phase, focused more on feasibility, dosing, and toxicity.[11-14] Thus, clinicians must explain the difference between preliminary trial design and later phases relying on existing experimental data. This distinction is especially challenging for patients in the setting of precision oncology due at least in part to the rapid incorporation of new research data into clinical therapy. The incorporation of seamless drug development strategies may circumvent traditional trial phases by adding additional cohorts to promising ongoing trials, further obfuscating how to frame expectations.[8,15]

Expectations and Consent

During the consent process for these trials, it can be challenging to manage expectations when the goal of precision medicine – personalized response – limits our ability to predict outcomes for any given patient. It has been such an obstacle that the field has replaced the term "personalized medicine" with "precision medicine": a characterization of the genetic risk and targeted therapeutic options for subpopulations rather than for subjects/patients themselves.[16] While "exceptional responders" have been identified and frequently publicized, these patients still represent the elusive outcome.[14] As such, much of the informed consent process requires assessing potential participants' expectations of cure and tempering them considerably.

It seems that in spite of our most honest disclosure of facts, a patient's choice to become a subject is likely to represent optimism rather than altruism.[17] The empiric literature demonstrates that the therapeutic misconception is more complex than subjects simply misunderstanding intent, and instead reflects patient's innate beliefs and hopes irrespective of statistics.[18] Nevertheless, potential exploitation is problematic. Given the inherent nature of precision medicine trials, how do we extrapolate one patient's outcomes (the N=1 dilemma) when counseling subjects? Of particular concern with advanced disease, enrolling in a precision medicine research protocol may exhaust precious time without guarantee, not only of outcome, but even of a therapeutic option. In addition to the potential toxicities and unknown benefit from novel targeted agents, delaying cancer-directed therapy may lead to unwarranted harm. Emerging data reiterates the downstream toxicities of such therapies that may persist, including formidable autoimmune consequences of immunotherapy.

While largely beyond our scope, tumor sequencing performed off-trial eliminates conflicting research versus clinical goals, but may engender formidable out-of-pocket expenses

compounding unrealistic expectations.[19] Many patients facing metastatic cancer are best served by palliative care and foregoing further cancer-directed therapy. But the unmet promise of precision oncology and other advances such as cancer immunotherapy may convince patients that a new drug or trial is a better bet.[20] Our job as clinicians and researchers is not to dissuade or de-emphasize trials or cancer-directed therapies, but rather to select potential subjects based primarily upon their own best interests, preferences, and reflective of their intense vulnerability. In many cases, acceptance of supportive care alone is indeed the appropriate choice.

Ultimately, potential subjects and patients should be counseled that in most cases, the use of genomics to identify personalized actionable targets is still in the exploratory phase of clinical research, and that precision medicine's benefit remains elusive. How the regulatory environment will evolve with the science also remains to be seen. Empirical studies are needed to explore and reframe patient expectations for benefit from precision oncology trials and clinical care. We are challenged to honestly, clearly, and compassionately engage a patient population in a challenging informed consent process that reflects their vulnerability, as well as ever-evolving evidence. This new era requires a continual reassessment of expectations and goals from both sides of the bed.

References:

1. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* Jun 30 2011;364(26):2507-2516.
2. Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) Mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. *J Clin Oncol.* May 20 2011;29(15):2121-2127.
3. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* Mar 15 2001;344(11):783-792.
4. Massard C, Michiels S, Ferte C, et al. High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial. *Cancer discovery.* Jun 2017;7(6):586-595.
5. Henderson GE, Churchill LR, Davis AM, et al. Clinical trials and medical care: defining the therapeutic misconception. *PLoS medicine.* Nov 27 2007;4(11):e324.
6. Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. *The New England journal of medicine.* Oct 25 2012;367(17):1616-1625.
7. del Carmen MG, Joffe S. Informed consent for medical treatment and research: a review. *The oncologist.* Sep 2005;10(8):636-641.
8. Hallowell N, Cooke S, Crawford G, Lucassen A, Parker M. Distinguishing research from clinical care in cancer genetics: theoretical justifications and practical strategies. *Soc Sci Med.* Jun 2009;68(11):2010-2017.
9. Altheide, DL. & Johnson, JM. "Criteria for assessing interpretive validity in qualitative research." In NK Denzin and YS Lincoln (Eds.) Handbook of Qualitative Research 1994.Thousand oaks, CA: Sage Publications (pp. 485-499).
10. Coyne IT. Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries? *Journal of advanced nursing.* Sep 1997;26(3):623-630.
11. Le Tourneau C, Delord JP, Goncalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol.* Oct 2015;16(13):1324-1334.
12. NCI-MATCH: Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma. 2016; https://clinicaltrials.gov/show/NCT02465060.
13. Morris LG, Chandramohan R, West L, et al. The Molecular Landscape of Recurrent and Metastatic Head and Neck Cancers: Insights From a Precision Oncology Sequencing Platform. *JAMA Oncol.* Jul 21 2016.
14. Beltran H, Eng K, Mosquera JM, et al. Whole-Exome Sequencing of Metastatic Cancer and Biomarkers of Treatment Response. *JAMA Oncol.* Jul 2015;1(4):466-474.

5. Prowell TM, Theoret MR, Pazdur R. Seamless Oncology-Drug Development. *The New England journal of medicine.* May 26 2016;374(21):2001-2003.
6. Juengst E, McGowan ML, Fishman JR, Settersten RA, Jr. From "Personalized" to "Precision" Medicine: The Ethical and Social Implications of Rhetorical Reform in Genomic Medicine. *Hastings Cent Rep.* Sep 2016;46(5):21-33.
7. Sulmasy DP, Astrow AB, He MK, et al. The culture of faith and hope: patients' justifications for their high estimations of expected therapeutic benefit when enrolling in early phase oncology trials. *Cancer.* Aug 01 2010;116(15):3702-3711.
8. Weinfurt KP, Seils DM, Lin L, et al. Research participants' high expectations of benefit in early-phase oncology trials: are we asking the right question? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Dec 10 2012;30(35):4396-4400.
9. Yu PP. Challenges in Measuring Cost and Value in Oncology: Making It Personal. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* Jul-Aug 2016;19(5):520-524.
0. Yang Y, Pang Z, Ding N, et al. The efficacy and potential predictive factors of PD-1/PD-L1 blockades in epithelial carcinoma patients: a systematic review and meta analysis. *Oncotarget.* Nov 08 2016;7(45):74350-74361.