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Brief Communications

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 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. ***The Oncologist*** 2018;23:386–388

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 multidisciplinary 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 to comprehend 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, makes this more difficult to reconcile. There is currently a dearth of data exploring these themes in precision oncology, although empirical studies are ongoing [9]. In response, the National Cancer Institute has elicited

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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 are early phase, focused 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 and patients themselves [16]. Although "exceptional responders" have been identified and frequently publicized, these patients still represent an 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 empirical literature demonstrates that the therapeutic misconception is more complex than subjects simply misunderstanding intent and instead reflects patients' 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 of novel targeted agents, delaying cancer-directed therapy may lead to unwarranted harm. Emerging data reiterate that downstream toxicities of such therapies may persist, including formidable autoimmune consequences of immunotherapy.

Although 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 and preferences and reflective of their intense vulnerability. In many cases, acceptance of supportive care alone is indeed the appropriate choice.

Conclusion

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 an 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.

Disclosures

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For Further Reading:

Fortunato Ciardiello, Richard Adams, Josep Tabernero et al. Awareness, Understanding, and Adoption of Precision Medicine to Deliver Personalized Treatment for Patients With Cancer: A Multinational Survey Comparison of Physicians and Patients. ***The Oncologist*** 2016;21:292–300.

Implications for Practice:

Two surveys were conducted to evaluate the global use of biomarkers in clinical practice and the largely unreported patient experience of precision medicine. These findings are especially relevant because they address both self-reported and physician-assessed levels of patients' "cancer literacy." This unique opportunity allowed for identification of areas where patients and physicians are communicating effectively, and also where there is a teachable gap in patient education. Furthermore, surveying physicians about the advantages and roadblocks they experience with biomarker testing provided valuable information on ways to improve the delivery of precision medicine to provide personalized care and ultimately enhance patient care.