

Right-to-try laws and individual patient “compassionate use” of experimental oncology medications: A call for improved provider-patient communication

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ABSTRACT

The U.S. Food and Drug Administration’s Expanded Access program allows patients with life-threatening diagnoses, such as advanced cancer, to use experimental medications without participating in clinical research (colloquially, “Compassionate Use”). Sixteen U.S. states recently passed “right-to-try” legislation aimed at promoting Expanded Access. Acknowledging popular support, Expanded Access could undermine clinical trials that benefit public health. Moreover, existing norms in oncologic care, for example, often lead patients to pursue intense treatments near the end of life, at the expense of palliation, and improved communication about the risks and benefits of Expanded Access would more often discourage its use.

Patients with life-threatening cancer diagnoses face numerous healthcare decisions that have implications for quality of life and longevity. In the United States, new medications are not publicly available until they have been tested in Phase III clinical trials, shown evidence of safety and efficacy, and gained approval from the Food and Drug Administration (FDA, 2013). When standard anticancer treatments fail, patients may want to use new medications that are not yet publicly available by participating in a clinical trial, particularly if results from earlier phases of the research are promising. However, some patients may not meet the specific eligibility criteria for a particular trial or live too far away to participate. Acknowledging that patients with life-threatening illnesses who are ineligible for research studies may be unable to wait months or years for medications to proceed to FDA approval, the FDA offers an individual-patient Expanded Access program, colloquially referred to as “Compassionate Use.” The program sets criteria by which patients with life-threatening illnesses can gain access to experimental medications before they are approved for public use and without participating in clinical research (FDA, 2013).

Out of compassion for patients with life-threatening diagnoses, there have been calls for changes aimed at making Expanded Access to experimental medications even easier (Andrews, 2014; Begg, Kim, & Neaton, 2014; Servick, 2014). For example, in the past 1.5 years, 16 U.S. states have passed “right-to-try” laws aimed at further deregulating access to experimental medications

(Gaffney, 2015). In contrast, critics of Expanded Access (Kesselheim, Tan, Darrow, & Avorn, 2014; Roth-Cline & Nelson, 2014; Walker, Rogers, & Entwistle, 2014) have suggested that it poses complex ethical tradeoffs: It may benefit individual patients, while potentially undermining research that benefits society. This review reiterates those concerns, while arguing that the benefits for patient care are potentially dubious, given the risks of experimental oncology medications and the known benefits of palliative cancer care. Therefore, rather than easing access, this review instead calls for improved provider-patient communication about the risks and benefits of Expanded Access to experimental oncology medications, thereby discouraging its use.

Background on the expanded access program

To use the Expanded Access program, patients would need to consult with their physician, submit an application to the FDA for potential authorization, and work with the pharmaceutical company to acquire the medication for personal, not research, use (FDA, 2013). To gain FDA authorization, the treating physician and the FDA must agree that (a) the patient has a serious or life-threatening condition and lacks other alternatives, (b) the potential benefits outweigh the risks, and (c) and the patient’s use of the medication will not interfere with clinical trials. Each of these criteria is open to interpretation. For example, although evidence from late Phase II, or even Phase III trials, is needed to

support the benefit–risk ratio, there are no explicit criteria regarding the level of evidence necessary (Brower, 2014).

The application to the FDA is completed by the physician and/or pharmaceutical company in conjunction with the petitioning patient. The application, which takes approximately 8 hr to complete (Darrow, Sarpatwari, Avorn, & Kesselheim, 2015), requires a rationale for using the Expanded Access program, information on the patient's health status and the medication (i.e., administration procedures, pharmacology, toxicology, reasonably safe dose and duration, monitoring procedures, the manufacturing facility), and the names of the physician and sponsor, and their agreement to comply with regulatory responsibilities (e.g., gaining full-board institutional review board [IRB] approval, submitting annual reports). The IRB requirement is unusual as the patient does not participate in the clinical trial, and although there is some required reporting of adverse events, the intent appears to be provision of care, rather than producing generalizable knowledge (the IRB definition of “research” under U.S. regulations). The pharmaceutical company must also indicate how much patients are expected to pay for the medication, though charges are restricted to the direct production costs and usually waived entirely (Chapman, 2014). In this process, the FDA has typically played only a superficial role in decision making. Namely, in recent years the FDA has received approximately 1,000 applications per year and approved about 99.5% of these (Kesselheim et al., 2014; Servick, 2014).

Thus, the key decision point is whether patients (and their families) and physicians pursue the process (Brower, 2014). The phenomenology of Expanded Access (e.g., who initiates the process, why, what diseases are treated) warrants further attention. It has been suggested that Expanded Access is mainly sought by highly active patients who have the time, resources, and educational skills needed to extensively research treatment options and navigate a challenging healthcare system (Brower, 2014; Darrow et al., 2015; Goodman, 2014; Magnus, 2014). Given that providers play a key role in enrolling patients in clinical trials, one might wonder whether they are often involved in initiating applications for Expanded Access. As the application process and reporting requirements place significant burdens on providers, historically they have acted less as initiators and more as gatekeepers (Darrow et al., 2015) who can communicate the risks and benefits of Expanded Access to enquiring patients and encourage or discourage its use.

In the United States, several factors suggest that the public generally supports Expanded Access. From

2014 through April 2015, 16 U.S. states have passed right-to-try laws that have aimed to facilitate Expanded Access by allowing patients and their physicians to bypass the FDA's regulatory authority to seek experimental medications directly from pharmaceutical companies (Andrews, 2014; Begg et al., 2014; Gaffney, 2015; Servick, 2014). Another 23 U.S. states are currently considering right-to-try legislation (Gaffney, 2015). These laws are essentially symbolic because they are trumped by federal regulations (Servick, 2014), but nonetheless suggest growing public awareness and support. Why are initiatives, such as Expanded Access and right-to-try laws, so popular? At their core, these initiatives are grounded in the ethical principle of respect for patient autonomy (Gesme, 2007) and, thus, appeal to the nation's deeply-held belief in individualism (Walker et al., 2014). Cross-cultural research also suggests that it appeals to how Americans define “hope” in medically dire situations, namely as hope for continued scientific breakthroughs (Del Vecchio Good, Good, Schaffer, & Lind, 1990). Beyond appeals to autonomy and hope for a cure, there may be other factors at play that warrant empirical attention, such as societal or family pressures, the increased social support offered by kind medical staff, the hope that a positive result could inform new lines of research, or a desire to reclaim power in what may feel like a very powerless situation. Thus, although there are many potential reasons for the popularity of Expanded Access, the myriad drawbacks are increasingly being discussed.

Critics (Kesselheim et al., 2014; Roth-Cline & Nelson, 2014; Walker et al., 2014) traditionally have argued that although Expanded Access may afford benefits to individual patients, it allows the patients to use the medications without participating in clinical research. Thus, if widely adopted, Expanded Access could undermine public health by diverting resources from randomized clinical trials, (Goodman, 2014; Kesselheim et al., 2014; Magnus, 2014; Walker et al., 2014) the gold-standard for evaluating experimental medications. Although the FDA's application process requires confirmation that the use of Expanded Access will not interfere with ongoing clinical trials (FDA, 2013), five lines of reasoning raise concerns. One, the FDA approves nearly all Expanded Access applications (Kesselheim et al., 2014; Servick, 2014), suggesting a low bar for evidence that ongoing trials are not being disrupted. Two, any particular research program has finite resources, and Expanded Access can shift staff time and resources away from conducting clinical trials toward monitoring individual nonresearch patients in the Expanded Access program (Goodman, 2014). Three, as some pharmaceuticals are expensive or challenging to develop in large

quantities, Expanded Access can also shift available pharmaceutical supplies away from clinical trials toward individual patients (Goodman, 2014). Four, in the long-run the Expanded Access program has the potential to disincentivize research by making it easier for patients and their physicians to access experimental medications outside of research, thereby hindering the development of new medications that could more broadly benefit society (Walker et al., 2014). Five, some have raised concerns that in the long-run pharmaceutical companies could co-opt the Expanded Access program as a means of marketing pharmaceuticals directly to consumers (Goodman, 2014; Walker et al., 2014), thus bypassing the FDA's regulatory authority to ensure that available pharmaceuticals meet basic standards of safety and efficacy. To date, these risks are mainly theoretical (Rabourn & Bedlack, 2014), though there have been some examples of clinical trials being disrupted by the Expanded Access program (Walker et al., 2014). The frequency of these disruptions is unknown but troubling given that the FDA's application process is designed to prevent them.

In addition to disrupting the process of conducting clinical trials, Expanded Access has the potential to undermine the approval of potentially efficacious medications that could otherwise more broadly benefit society (Caplan & Bateman-House, 2014; Kesselheim et al., 2014; Walker et al., 2014). The Expanded Access program makes medications available to patients who, by definition, do not meet the eligibility criteria for a clinical trial. If researchers have selected the eligibility criteria largely for scientific reasons, rather than merely out of convenient access to a particular patient population, then Expanded Access may facilitate patients' use of medications that are contraindicated, such as a patient with comorbid heart disease using an experimental oncology medication that increases risk of a pulmonary embolism (Caplan & Bateman-House, 2014). Although individual patients with life-threatening cancer diagnoses may be willing to assume the risks of taking an experimental and potentially contraindicated medication, adverse events, however anecdotal, could derail the eventual approval of medications, either by discouraging pharmaceutical companies from proceeding with development or by leading the FDA to deny approval (Chapman, 2014; Kesselheim et al., 2014; Walker et al., 2014). In summary, prior reviews have duly noted the potential for Expanded Access to disrupt scientific research that is designed to benefit public health.

Controversies in the provision of patient care

Beyond the societal costs, available evidence raises questions about the extent to which Expanded Access

affords benefits to individual patients participating in the program. Although the FDA's application process states that the authorization of individual-patient Expanded Access requires evidence that the potential benefit justifies the risks (Brower, 2014), the FDA only denies a handful of applications each year (Kesselheim et al., 2014; Servick, 2014), arguably functioning as a de facto rubber stamp regardless of the risk-to-benefit ratio (Brower, 2014). There have been no studies directly quantifying the risks and benefits of participating in the Expanded Access program. Nonetheless, because Expanded Access patients are seeking medications currently being evaluated in clinical trials (typically late Phase II or Phase III), some rough inferences about the potential risks and benefits can be gleaned from meta-analyses of clinical trial outcomes.

Although there have been meta-analyses of individual patient outcomes (e.g., complete response, severe toxicities) in Phase I (dosage) trials (Horstmann et al., 2005), there are no comparable studies for Phase II and III (safety and efficacy) trials. In Phase I trials of single-agent cytotoxic chemotherapies, 15.0% of participants experience at least one Grade 4 (life-threatening) toxicity and 0.6% die from toxic events (Horstmann et al., 2005). There are no known meta-analyses of Grade 3 toxicities in clinical trials at any stage, though presumably these occur more frequently than Grade 4 toxicities. Examples of Grade 3 toxicities include severe diarrhea (≥ 7 stools per day over baseline, IV fluids for ≥ 24 hours, hospitalization), severe vomiting (≥ 6 episodes in 1 day, IV fluids for ≥ 24 hours), and severe cardiac arrhythmias (e.g., leading to a loss of consciousness, requiring a defibrillation, or requiring a pacemaker; National Cancer Institute, 2010). Relative to Phase I trials, it is difficult to know whether toxicities are more common in Phase II and III trials (since average doses are higher) or less common (since only more encouraging medications progress to those phases). Using common dosage rules, such as the traditional 3 + 3 design (Le Tourneau, Lee, & Siu, 2009), dosages for Phase II trials are often set at levels that were found to cause severe (Grade 3 or 4) toxicities among one-in-six participants (16.7%) in the Phase I samples, so the potential for severe side effects remains considerable in later stages of pharmaceutical development. Given that Expanded Access patients are generally more severely ill than clinical trial participants, it has been suggested that they are considerably more vulnerable to toxicities (Caplan & Bateman-House, 2014; Chapman, 2014; Gesme, 2007; Walker et al., 2014). In summary, although there are many uncertainties surrounding the risks of participating

in Expanded Access, available evidence suggests that side effects have the potential to be debilitating.

Meta-analyses from clinical trials can also help to draw loose inferences about the potential benefits of Expanded Access. In Phase I trials of single-agent cytotoxic chemotherapies, approximately 1.5% of patients experience a complete response (Horstmann et al., 2005), and this rate is presumably higher (though to an unknown degree) in Phase II and III trials, given that more promising pharmaceuticals are more likely to progress to later phases of development (Hay, Thomas, Craighead, Economides, & Rosenthal, 2014), and given that participants in later trials receive the maximum tolerated dose (instead of some receiving lower doses, as in Phase I trials) (Le Tourneau et al., 2009). Recently, Hay et al. (2014) examined the proportion of experimental medications ultimately gaining FDA approval, with estimates provided separately by phase of the research as well as for different classes of medications. They found that only 10.5% of oncologic medications in Phase II trials and 37.0% in Phase III trials ever ultimately received FDA approval. The proportion of individual patients experiencing benefit from oncologic medications in Phase II and III trials is likely considerably lower than the overall FDA-approval rate, given that not all FDA-approved medications help all patients. Thus, for patients receiving oncologic medications in Phase II trials, the complete response rate is likely somewhere between 1.5% and 10.5%, whereas the rate is likely between 1.5 and 37.0% in Phase III trials, an admittedly broad interval. Moreover, these medications are less likely to benefit patients in the Expanded Access program than those in clinical trials, as Expanded Access patients are more likely to be very ill, have comorbid conditions, and fail to meet eligibility criteria predictive of presumed benefit (Caplan & Bateman-House, 2014; Chapman, 2014; Gesme, 2007; Walker et al., 2014).

Clearly, some patients might justifiably prefer to receive an experimental medication through Expanded Access. Expanded Access might be more justifiable for individual patients when the patient is truly informed of the risks and benefits, is ineligible for the clinical trial for reasons other than their likelihood of experiencing benefit (e.g., excluded based on geographic location), relevant findings are available from late Phase III trials supporting efficacy, known toxicities of the medication are low, and the patient has a good functional status that would facilitate withstanding toxicities. There are no known data on the clinical characteristics of patients seeking Expanded Access, but the frequency with which patients with life-threatening cancer diagnoses receive intensive treatments near the end of life in the United

States suggests that the above justifications may frequently be overlooked (Goodman, Morden, Chang, Fisher, & Wennberg, 2013; Institute of Medicine, 2013, 2014; Temel et al., 2010).

In particular, existing norms in oncologic care for patients with life-threatening diagnoses bias patients toward more intense care (Institute of Medicine, 2013, 2014)—of which Expanded Access may be one example—at the expense of palliation. Effective communication of health information has been a long-standing challenge in oncologic care (Hoerger et al., 2013; Novack et al., 1979). Americans often conceptualize “hope” as meaning hope for a cure (Del Vecchio Good et al., 1990), despite that hope has many meanings (Coulehan, 2011), including hope for more realistic outcomes, such as good quality of life near the end of life. When conceptions of hope are tethered to a cure, providers can feel pressured to describe prognosis and the benefits of experimental treatments overoptimistically (Lamont & Christakis, 2001), continue to offer intensive treatment options when objective evidence suggests that it is frivolous (Walker et al., 2014), and avoid advising patients to discontinue further anticancer treatments out of fear of “abandoning” them (Gesme, 2007; Meier, 2014). Patients and families also feel pressure to pursue intensive treatments, given societal norms of maintaining a “fighting spirit” and “staying positive” about one’s chances (Epstein & Entwistle, 2014; Walker et al., 2014). These norms within the provider–patient–family triad can lead all parties to engage in “collusion” about the likelihood that further treatments will afford benefits to patients who are already very ill (The, Hak, Koeter, & van der Wal, 2000; Weeks et al., 2012). This routinely leads patients with life-threatening illnesses to overestimate the favorability of their prognoses, often dramatically (Parker et al., 2007; Weeks et al., 1998; Wright et al., 2008), as well as overestimate the likely benefits of intensive and experimental treatments (Mackillop, Stewart, Ginsburg, & Stewart, 1988; Sulmasy et al., 2010; Weeks et al., 2012). To the extent these norms hinder patients from being informed of the real risks of their treatments, they can bias patients toward pursuing aggressive care, including gaining Expanded Access to experimental medications.

Contrary to these long-standing norms, there have been numerous calls in recent years emphasizing the importance of both avoiding overtreatment and providing palliative services in the final months of life (Institute of Medicine, 2013, 2014; Smith et al., 2012). By default, many patients with life-threatening diagnoses receive aggressive treatments that reduce quality of life without foreseeable benefit, such as chemotherapy in the final two weeks of life (Goodman et al., 2013;

Institute of Medicine, 2013, 2014; National Comprehensive Cancer Network [NCCN], 2013; Temel et al., 2010). In this context, medication toxicities often result in needless ICU visits and hospitalizations. For example, in a recent study of over 200,000 Medicare beneficiaries who died of cancer (Morden et al., 2012), 48.1% were found to have seen ≥ 10 physicians in their final 6 months of life, 64.9% had an inpatient hospitalization in their final month, and 24.7% had an ICU visit in their final month. As well, 30.2% of patients died while hospitalized, rather than at home where most patients prefer.

Similarly, referrals to palliative care and hospice services often occur much too late to provide substantial benefit, if the referrals occur at all (Institute of Medicine, 2013, 2014; Temel et al., 2010). This is unfortunate because numerous intervention studies have shown that palliative approaches to care for patients with life-threatening diagnoses foster better physical quality of life and reduce depressive symptoms (Parikh, Kirch, Smith, & Temel, 2013; Temel et al., 2010; Zimmermann, Riechelmann, Krzyzanowska, Rodin, & Tannock, 2008; Zimmermann et al., 2014). Palliative care programs are rapidly expanding in the United States, Canada, Europe, and Australasia (Institute of Medicine, 2014), and a recent ground-breaking randomized controlled trial (Temel et al., 2010) found that relative to usual care, patients with nonsmall-cell lung cancer assigned to early palliative care lived an average of 2.5 months longer, contrary to the notion that palliation hinders longevity. Similarly, a recent follow-up study involving a heterogeneous sample of patients with advanced cancer found that early palliative care increased survival by 6.5 months, relative to delayed palliative care (Bakitas et al., 2015). Several guidelines (Institute of Medicine, 2013, 2014; NCCN, 2013; Smith et al., 2012) have recently called for the greater integration of palliative care into standard oncologic practice, and the Commission on Cancer now includes the meaningful integration of palliative care services in their accreditation standards (American College of Surgeons, 2012). To the extent Expanded Access to experimental medications induces toxicities and deters patients with life-threatening cancer diagnoses from receiving palliative services, it represents a form of aggressive care that may be at odds with emerging standards in oncology.

Need for compassionate provider-patient communication

Acknowledging differing views (Kesselheim et al., 2014; Walker et al., 2014; Wicks & Heywood, 2014), this review argues that the limitations of Expanded

Access—both for the scientific research underlying public health and for individual patients—suggest that its use should generally be discouraged, reserved only for a very limited number of cases where the presumed benefit is clear. The FDA has historically exerted little de facto power in regulating Expanded Access (Kesselheim et al., 2014; Servick, 2014), and many Americans have a viscerally negative reaction to governmental intervention into individual healthcare decisions, particularly pertaining to end-of-life care (Nyhan, 2010). Accordingly, intervening at the level of the provider-patient relationship might be more tenable for reducing use of Expanded Access, as Americans deeply value the sanctity of that relationship in making healthcare decisions (Eveleigh et al., 2012).

In particular, there is a need for improved provider-patient communication aimed at helping patients with life-threatening cancer diagnoses and their families to understand the risks and benefits of Expanded Access. Existing norms in oncologic care promote over-optimistic interpretations of the risks and benefits of further treatments for patients who are very ill (Mackillop et al., 1988; Parker et al., 2007; Sulmasy et al., 2010; Weeks et al., 1998; 2012; Wright et al., 2008), ultimately contributing to the use of intensive treatments that can make one's final months much more debilitating (Morden et al., 2012). Even when individual providers give realistic information about the risks of further treatments, patients with life-threatening diagnoses are often still exposed to so much overly optimistic information from other providers, friends, and family, it can be difficult for realistic information to penetrate (Wolf & Wolf, 2013). Consequently, Wolf and Wolf have called for “compassionate persistence,” meaning that providers should exercise persistence in describing, reflecting, and repeating the risks and limited benefits of further anti-cancer interventions. This persistent approach recognizes that patients can make truly informed decisions only when the risks and benefits have been fully absorbed.

Simultaneously, it can be useful for providers to clarify several key facts about palliative care. About 80% of American adults report not knowing what palliative care is (Institute of Medicine, 2014). Moreover, patients and providers often view palliative care as scary, “giving up,” or equivalent to hospice care (Gerhart et al., *in press*; Institute of Medicine, 2014; Lo, Quill, & Tulsky, 1999), which may explain why most patients with advanced cancer in the United States never use palliative care or only do so after substantial delays (Institute of Medicine, 2014; Osta et al., 2008). Foremost, it should be noted that in the United States, palliative care is different from hospice care (Institute of

Medicine, 2013, 2014). Although palliative care focuses on improving quality of life, it can be provided concurrently with anti-cancer treatments, and is more effective when provided early in the course of the illness, which is what the American Society of Clinical Oncology now recommends (Smith et al., 2012). In these ways, palliative care differs from the more specialized hospice care programs in the United States, which are solely for patients with less than 6 months to live and require forgoing anticancer treatments (Institute of Medicine, 2014). As well, it could be useful for providers to emphasize that palliative care does not hasten death, and two recent high-quality randomized controlled trials suggest that palliation may actually prolong life (Bakitas et al., 2015; Temel et al., 2010). These conversations require compassionate communication, and future studies should examine interventions for enhancing communication and decision making in cancer care. Potential approaches might include the use of health coaches and standardized patient instructors to assist patients and providers in practicing communication skills in key areas, such as discussing prognosis and health information, expressing and responding to emotions, and engaging in shared decision making (Hoerger et al., 2013). As well, medical education programs are increasingly being adapted to train these skills (Back et al., 2007), and decision aids may also be useful for increasing patient understanding of palliative care (Hoerger et al., 2015).

In closing, the Expanded Access debate raises questions about what constitutes compassionate care for patients with life-threatening cancer diagnoses. The Expanded Access program has scientific drawbacks for public health and may have dubious benefits for individual patients. Improved oncologic communication about the risks and benefits of experimental medications is vital to compassionate care and would more often discourage use of the Expanded Access program.

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