Right to Try Act: A Pediatric Oncology View Point

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Introduction and Right to Try Act

Right to try laws was passed to assist terminally ill patients with access to investigational therapies (drugs/compounds, biologics, or devices) that have not been approved for commercial marketing by the FDA (Figure 1) [1]. Colorado was the first state to pass a right-to-try law in 2014. Subsequently, as of August 2018, 41 states had enacted such laws [2]. On May 30, 2018; President Trump signed a federal Right to try law. There remains considerable controversy amongst many groups about the potential benefit of such laws or the potential harm that these efforts provide to patients, including false hope that unproven therapies will provide [3]. There is a general feeling amongst some groups that “deregulation is a cure for everything”, and thus removing the FDA from the process of gaining access to investigational therapies will expedite the approval of such therapies and bring curative therapies to patients who are terminally ill. These and other issues will be discussed in this review.

Pediatric Oncology: Overall Survival and Short & Long-Term Concerns

The field of Pediatric Oncology includes not only the treatment of solid tumors but also the treatment of liquid tumors such as Hodgkin Lymphoma, non-Hodgkin lymphomas and the leukemia’s including myelodysplastic syndrome as well. In fact, Acute Lymphoblastic Leukemia (ALL) is the most common malignancy that occurs in the pediatric and adolescent age group [4]. Because the results of many investigational trials have contributed very significantly to the treatment progress that has been made over the past 40 years and because these trials are usually multi-year in duration just in terms of actual treatment, it usually takes a few years after a trial has completed enrollment that we view the results of a comparative nature. In a recent publication by Smith and his colleagues, overall five-year survival for a mixture of malignancies that occur in the pediatric and adolescent aged group hovers 80% to 90% (Figure 2) [4]. As detailed in the 2014 manuscript, five-year survival may be higher with certain specific malignancies and lower with others. In addition, relapses or recurrent disease development may occur more than five years after the initial diagnosis. Regardless, this still leaves 1 in 10 to 1 in 5 children with malignancies who do not respond long-term to the standard approved and conventional treatments. It is this group of patients for which an enormous effort is expended to find curative therapies and it is for this group of patients that the right-to-try legislation was initially proposed [5,6].

In addition, as shown in Figure 3, there is overall concern with the short and long-term effects of the curative therapies that have been provided. It is the hope that with the development of newer therapeutic strategies for those who relapse from their primary malignancy or develop a recurrence while under treatment will come less toxic treatments that over time provide the same curative
potential. Many of the current compounds that form part of the standard therapies for various malignancies were first used for those with relapsed or recurrent disease. When the final doses were set and the adverse effects better understood, these compounds that once were “investigational” were moved up to first line therapies and were compared in randomized controlled trials to determine if the use of these “newer” therapies could help to advance treatment progress.

### Off Label Use of Compounds

Off label use involves the Health Care Provider (HCP) prescribing medications for indications not approved by the FDA [7]. In addition, off label use may also apply to using a dosage or dosage form that also has not been approved by the FDA. The FDA does not control how medications may be prescribed once they are approved and marketed. It has been estimated that in some specialties, off-label use may be as high as 47%. In oncology, the off-label use may be as high as 50% [8]. An off-label use for a given drug may become a widely accepted practice or even a standard of care.

What is the difference between the off-label use of a medication and the use of an investigational compound not yet approved by the FDA for any indication? This is an interesting question that has only partially been discussed in the medical literature [8]. FDA does not permit the marketing of products for off-label use, nor does the FDA permit the marketing of investigational products not yet approved.

Since the FDA does not control how marketed medications may be used by HCPs, sometimes off-label use of some medications may become an accepted practice well documented in the medical literature despite the fact that manufacturer of the medication may not have conducted the clinical trials leading to a supplemental application for a new indication. An investigational medication would never become an accepted practice since the manufacturer of the product would not be permitted to distribute and market the product without an FDA approved indication.

Physicians in general inform patients when they are using a product in an off-label manner and often have to seek insurance approval, particularly for very expensive therapies [8]. It has been suggested that physicians prescribing a medication off-label should be well informed about the medication, particularly the potential adverse effects, and have a good scientific rationale for the use of the product. From a legal point of view, it is not clear that the HCP needs to obtain written consent from a patient for an off-label use and if an Institutional Review Board (IRB) must consider the off-label use of an approved medication for an individual patient [8].

The Right to Try Act was enacted to enable patients to have potential access to compounds under development [9,10]. However, patients and/or their HCPs must be aware of the compounds under development that may have a therapeutic potential for a specific disease. This information is not easy to ascertain. Usual sources of information include www.clinicaltrials.gov, a website maintained by NIH on which most clinical trials are registered. Searching this site requires the use of “key words”, which is not always as straightforward as it may sound. In addition, the internet and patient advocacy groups may be a good source of information on compounds under investigation as well, both for the patient and the HCP. In addition, the HCP may have other physicians in his/her network available for consultation.

However, equally as important may be access to medications/compounds already developed and on the market for a particular indication, but for which there may be medical literature and knowledge available about other uses outside of the approved indication (off label). This information may not likely be well known to a patient’s HCP and thus the internet, medical literature searches, patient advocacy groups and alternative physician consultations all may be sources of information on other medications/compounds that may have potential therapeutic usefulness. The use of a medication off-label might potentially take less time to prescribe than obtaining access to an investigational agent from the manufacturer [8]. In addition, even though some malignant diseases are different, they may share common targets or mutations, affording the possibility of using a drug that was initially indicated for one malignancy with the potential access to compounds under development [9,10]. However, equally as important may be access to medications/compounds already developed and on the market for a particular indication, but for which there may be medical literature and knowledge available about other uses outside of the approved indication (off label). This information may not likely be well known to a patient’s HCP and thus the internet, medical literature searches, patient advocacy groups and alternative physician consultations all may be sources of information on other medications/compounds that may have potential therapeutic usefulness. The use of a medication off-label might potentially take less time to prescribe than obtaining access to an investigational agent from the manufacturer [8]. In addition, even though some malignant diseases are different, they may share common targets or mutations, affording the possibility of using a drug that was initially indicated for one malignancy with that target or mutation [11]. The better understanding of cancer biology and molecular information has guided pediatric oncologists to use drugs initially approved for an “adult-type” malignancy in the treatment of a pediatric patient because the target and/or mutation are similar even though the histology of the malignancy may be quite different from the initial approval [11].

Both the potential access to an investigational compound through the Right to Try Act, participation in an expanded access study with a compound approved by the manufacturer for such use or the use of an off-label medication all involve a time commitment on the part of the patient and the patient’s HCP. For each individual patient it is impossible to estimate the amount of time that might be expended
in total by all involved for an alternative therapy once the patient has failed the primary or standard therapies. But it is fair to say that the time spent may be measured in hours.

Expanded Access

Expanded access is the use of an investigational compound or device outside of an established clinical trial [12-15]. Usually the use of an investigational compound or device is to diagnose, monitor or treat patients with serious or life-threatening diseases. For a variety of clinical reasons, patients and/or their HCPs will have decided that there are no satisfactory therapy options available. Considering the enormous progress that has been made over the years in the field of pediatric oncology by pediatric patients and their HCPs participating in clinical trials, it is preferred that a patient receive an investigational compound as part of a clinical trial. However, patients may not be able to receive an investigational compound if trial enrollment is not yet available for patient recruitment or the appropriate trials are closed to patient recruitment or clinical trials are not available (either due to restrictions on patient access due to inclusion criteria or the patient and/or family/significant others are unable to travel to a center at which an investigational compound may be available).

To initiate the process of access to an investigational compound outside of a clinical trial, the patient and/or HCP contacts the pharmaceutical or biotech company developing the compound to determine if the company has an expanded access protocol (sometimes referred to as a “compassionate use” protocol) [15]. If not, the inquiry then focuses on whether the company will still provide the investigational compound. There is no legal requirement that a company has to provide an investigational compound to an individual patient outside of any clinical trials in place, that are approved by the FDA, nor is there any legal requirement that a company has to provide an investigational compound even if clinical trials have yet to begin. Some products under development may be in such supply that the manufacturer has an insufficient supply available for expanded access. In addition, the manufacturer may not desire to supply an investigational medication when insufficient toxicity/safety data are available by their determination.

Once a company has issued a Letter of Authorization or has agreed in writing to provide the investigational compound for the patient in question, then a request is made to the FDA by the patient’s HCP for expanded access [12,13]. Form FDA 3926 can be used for this application [14]. Per the requirements of the Paperwork Reduction Act of 1995, it is estimated that it will take an average of 45 min to complete the responses required on FDA form 3926 [14]. FDA then has to determine the potential benefit to the patient that justifies the potential risks of using the potential investigational agent. It has been estimated that in recent year, 99% of the expanded access requests to the FDA have been approved [16]. If the patient requires the investigational compound on an emergency basis, a mechanism is in place for a phone approval; however, FDA form 3926 still has to be submitted. In all cases, Institutional Review Board (IRB) approval will be necessary. There is usually a well-established procedure for obtaining such approval in academic medical centers or other medical centers. For those HCPs in private practice requesting the use of an investigational compound through the expanded access program, IRB approval is usually through a local university, hospital or an independent IRB. Informed consent must be obtained before beginning treatment with any investigational compound.

In some cases, the company supplying the investigational compound may be able to charge for the compound [8]. Associated costs for the preparation, administration and monitoring of the treatment with the investigational compound may not be covered by Medicare, Medicaid or third-party payers. The HCP and the patient will have investigated the potential costs associated with the treatment with an investigational compound. If specific requirements are in place for monitoring patients receiving a specific investigational compound, these will need to be followed. Adverse events associated with the use of the investigational compound will need to be reported to the FDA and usually to the approving IRB [12,13].

Concerns about the Right to Try Act

On the surface, the Right to Try Act will permit terminally ill Americans to try investigational therapies not yet approved by the FDA. However, an ‘eligible investigational drug’, as defined in the Act, is one for which a Phase 1 clinical trial has been completed and/or is ‘the subject of an active investigational new drug application’ and ‘the active development or production of which is ongoing and has not been discontinued by the manufacturer or placed on a clinical hold’ [1]. Because of the position of the FDA in the approval process for investigational therapies, a patient treated by a HCP under the Right to Try Act does not have to complete any FDA related forms and does not have to contact the FDA to initiate such treatment [16]. However, the FDA may have advice that would be useful to the treated patient and/or the patient’s HCP that derives from the previously completed clinical trials including Phase 1 trials. Such information may be unpublished and confidential and not generally available. Thus, the patient and/or the HCP will not have an interaction with the FDA during which such clinical treatment information could have been provided. There is the concern raised by many that the successful completion of a Phase 1 study is not enough to ensure efficacy nor safety on its own [17,18]. Published figures indicate that fewer than 10% of drugs that enter Phase 1 end up as approved drugs and in oncology, that number falls to 5% [17,18]. This usually means that the potential benefit of these compounds is not confirmed in subsequent trials. Thus, there is the real possibility that the Right to try a drug that has only gone through Phase 1 testing may not have identified the extent of possible adverse events. Thus, patients may be provided with a false sense of hope and the real possibility of unexpected harm from an unrecognized side effect [16].

In addition, the use of an investigational therapy under the Right to Try Act does not eliminate the need for the patient to provide appropriate consent for the treatment. Depending on the center/clinic/hospital at which the investigational treatment is provided, IRB approved consent may be necessary for the patient to sign. Thus, the need for an IRB review has not been eliminated by the Right to Try Act. The formation of the consent form and the approval of the IRB or the chair of the IRB as the recognized representative of the IRB will need completion by the HCP seeking the investigational therapy for the patient in question. This is the same process as if the HCP had applied for use of an investigational therapy through the FDA expanded access program [12,13].

There are several administrative, legal and insurance related concerns about investigational therapies provided under the Right to Try Act. The Act stipulates that the manufacturer or sponsor of an eligible investigational drug must provide a summary of the doses provided and any known adverse events that the patient(s) experienced [1]. Manufacturers and/or sponsors may not be subject
to liability for providing an investigational drug, unless it is proven that there has been ‘reckless or willful misconduct, (or) gross negligence’, bypassing the oversight that the FDA ordinarily provides [1]. In addition, it remains untested as to whether insurers still need to cover medical expenses once a patient starts a drug under the Right to Try Act [16].

Several physician groups impacted by the Right to Try Act have formulated very clear position statements, most notably the American Society of Clinical Oncology [17,18]. For the reasons that already have been stated, the statement from ASCO indicates that the society does not support the Right to Try Act due to the potential harm to patients, the lack of the beneficial FDA oversight that comes with the expanded access program, and the fact that the Act does not increase the potential number of investigational therapies available to patients beyond what are already available through an expanded access program. The Right to Try Act does not coerce nor force nor compel any device or pharmaceutical company to make available an investigational therapy. Such device or pharmaceutical companies often have a variety of reasons for not making investigational therapies available on an expanded access basis due to #1 uncertainty about all the potential adverse effects or #2 emphasis on the use of the investigational therapies only in clinical trials and not outside of clinical trials, or #3 inadequate supplies of an investigational therapy beyond what is needed for clinical trials, or #4 lack of an important signal or result from early phase studies or first in human studies resulting in a lack of interest for any further use of development of the investigational therapy.

One recorded remark on the Right to Try Act passage is that the “only good to come from the Act is the increased awareness of the expanded access program” [10]. The sentiment is that patients should have increased access to investigational therapies, especially through established and approved clinical trials. In the absence of a clinical trial or for a variety of reasons the patient cannot participate in a clinical trial, then the expanded access program builds on the expertise of the FDA reviews of an application for expanded access of a particular investigational therapy. The FDA and patient advocacy groups may be able to assist with identifying those manufacturers with an expanded access program for an investigational therapy for a particular disease.

Comments made during Congressional debates on the Act include the following: “…(the Act would) provide fly-by-night physicians and clinics the opportunity to peddle false hope and ineffective drugs to desperate patients” and “the gullible will applaud (the passage of the Act)….patients will be targeted by unscrupulous snake oil sales people seeking profits” [10,18].

Role of Cooperative Groups and Pediatric Oncology Research Centers

The majority of children and adolescents with cancer are treated on clinical protocols. Such protocols are usually written and monitored by such large cooperative groups such as the Children’s Oncology Group or smaller innovative consortia of pediatric centers or such well known pediatric cancer centers at the Dana-Farber Cancer Center in Boston or the St. Jude Children’s Center in Memphis. Such investigational protocols often compare a standard approach to a novel approach or a new combination of therapies or the addition of a new therapeutic approach such as a new medication. As a result, patients and their HCPs can often short-circuit the search for either innovative investigational therapies or expanded access protocols or even potential off-label use of medications already marketed by consulting with colleagues in these groups or centers who share treatment information available for patients with particular oncology related problems with certain disease stages. In addition, there are quite a number of very active pediatric cancer advocacy groups, members of which maintain a high degree of interest in clinical investigations in the area of pediatric oncology and often have provided funds for particular research projects. As a result, many of the members of these advocacy groups keep in regular contact with many pediatric oncology clinical investigators and thus have information about specific treatments under investigation or particular protocols that are in place the knowledge of which might not be generally available or easily located on the internet.

What Choices Available for Patients without a Clear Path Forward

At the current time, there is no master list of all the compounds that are under investigation in the field of oncology that an HCP or a patient may access. Even if such a list existed, the list would be quite fluid with frequent changes, as new agents are added, and others deleted from the list having proven to be too toxic or not effective in Phase 1 or subsequent testing.

In addition, the repertoire of approved and marketed compounds used in oncology is at the current quite enormous, making it very difficult for any oncologist to have full and complete knowledge of how each and every one of these compounds have been used off label or are under use through an expanded access program. For each HCP and/or patient, there are four choices to complete a search for a potentially useful therapeutic product or combination: #1 consult with colleagues in the same practice or department or cooperative treatment group for information related to alternative treatments; or #2 review www.clinicaltrials.gov with an exhaustive search by disease and key words or review other materials posted on the internet; or #3 contact variety of patient related advocacy groups, particularly in the disease area of the patient, for suggestions and ideas of additional therapies worth considering; or #4 contact key pharmaceutical companies with deep pipelines in the oncology field and/or visit key scientific meetings with oncology related presentations to network with other HCPs, thought leaders, key opinion leaders and drug company representatives to search for potential suggestions for alternative treatments [19,20].

Conclusion

The Right to Try act presented a path forward for children, adolescent and young adults with relapsed or recurrent malignancies to access investigational medications that have completed phase 1 testing, but only if the manufacturer will release the medication for individual use as described. There may be many reasons why individuals may not access such medications through this route. Bypassing the FDA for approval and/or utilizing an investigational medication after early phase 1 testing may expose the patient to harm from either inadequate toxicity information derived from the early phase 1 testing or alternatively not have access to the toxicity/safety information residing with the FDA.

Consideration of the Right to Try Act however highlights the potential greater options of either expanded access trials already in place at a variety of medical/cancer centers to which the patient might have access or the various reported uses off-label of already marketed
oncology compounds that may have had favorable uses reported. In both these cases, access to FDA related information will potentially make the use safer of either the marketed but off-label compound or the compound approved for expanded access.

In all three scenarios (Right to Try, expanded access or off-label), the work of initiating the search for information, identifying potentially useful marketed or investigational compounds, and completing the requisite paper work will fall to the HCP and the patient. Various methods of short-circuiting this search were discussed, which will more quickly provide access to the relevant information.

References

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