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Cancer continues to claim the lives of more children than any other disease.. This statistic has not changed in more than 20 years. Even more disturbing is that the actual cure rates for children with myeloid leukemia, and solid tumors such as sarcomas, brain tumors and neuroblastoma have not improved. This is an unacceptable statistic for a disease that claims the life of so many of this country's youth. It robs us of future talent and tomorrow's leaders, tax payers and contributors.

Curing cancer requires new drugs. This is a fact. In the past 20+ years there have been numerous new agents approved to treat adults with cancer but only 1 new agent has been approved for children with cancer and that was chlofarabine in 2004. Pediatric oncologists are using the same drugs that we used 40 years ago.

Ironically, the first clinical trials combining several different chemotherapy drugs were used to treat children with leukemia. The pioneers in institutions in Memphis, Boston and Bethesda were told that combining these cytotoxic agents together would be too toxic and would kill patients.

But rather than kill, these combinations cured children who faced certain death. These children became survivors of childhood cancer. This concept of using combination chemotherapy for cancer treatment is what we use today for many different adult cancers. It was first in children, then in adults.

Yet today, children are being left behind with long delays or often no access to new drugs. What happened? Somewhere along the line we adopted an attitude of protecting children from toxicity rather than being *proactive* in finding them curative therapy. We have forgotten the lessons of the past. We have taken our eye off what I believe to be the goal of "***cure***" to one of "**fear of inducing toxicity**".

Fear of toxicity governs the FDA and paralyzes the pharmaceutical industry from including children early on in Phase I dose-finding, toxicity defining clinical trials. Phase I are first-in-human trials that use gradual increases in the dose of a new agent to establish the maximum tolerated dose and define the side effects of the drug at each dose.

These first-in-human Phase I trials are for patient >18 yrs. Once the dose is found, Phase II & III trials investigate efficacy in specific diseases and this data, if positive, is used to support approval. Children are not part of this scenario and thus do not have early access. There is no mandatory plan to include them. If the company wishes to investigate drug activity in children it must start the process of Phase I, II & III all over again, a time consuming and expensive process for a minute market.

It is the FDA's contention that it is not part of their jurisdiction to dictate to the pharmaceutical company how to design their trials. Their role is to advise, review and either approve/not approve. In my conversations with Pharma, I have been told over and over again that if even one child has an adverse reaction, the company **fears** that the FDA will suspend the approval process so they are reluctant to include children early on.

This is what paralyzes us and keeps us from getting new agents to treat childhood cancer. We need to adopt a more proactive attitude. Federal regulatory bodies need to shift their protective, toxicity adverse view when it comes to children with **cancer**.

Inclusion of patients < 18 years in the first-in-human Phase I trials is blocked because of the fear of side effects. But children with cancer who are eligible for Phase I trials, just like adults, are those with cancer that has not responded or has recurred following the most up-to-date, proven therapy regimens. These children are going to ***DIE***! There is no worse adverse drug reaction or drug-induced toxicity than death. Parents are perfectly capable of understanding the risks and making an informed decision. The concept that regulatory agencies must assume the guardianship and be the protector of children with refractory cancer is flawed. These children have an active malignant process consuming their bodies that will kill them. Nothing is less safe than death.

History has actually shown us that children are more tolerant not less tolerant to drugs than adults. And, when one considers the specific nature of the newer targeted cancer drugs aimed at specific pathways that tumors depend on, this shielding of children is not justified.

I have a modest proposal that I believe will take a small step toward rectifying this inequity.

Phase I trials start by using a low drug dose. After a few patients receive the drug at that dose without adverse effects, the next higher dose is given to another few patients. This goes on until the maximum tolerated dose is reached and the toxicity defined.

What I suggest is that a separate arm be built into Phase I trials with new anti-cancer agents for patients < 18years. The trial can be designed in this way. After the first dose level is completed and adult patients are entered onto the 2nd dose, Pediatric patients would be allowed to enter at dose level one. Once dose level one is shown to be safe the next cohort of Pediatric patients would be entered on the dose level that is one step BELOW where the adults are. That is to say if in the time it takes to complete dose level 1 assessment in children, that the adults are now on dose level 6, the next Pediatric patients would receive drug at dose level **5**, rather than dose level **2**, thereby skipping 3 dose levels. This would speed up the process of establishing the MTD for children. This would save resources for the company and speed up the process.

Pediatric oncologists could then decide which diseases to investigate in a Phase II trial. I suggest this design with confidence, it works. We showed this at MDA in a joint trial with the adult leukemia service where we established the MTD of clofarabine, the one new agent for Pediatric cancer that has been approved.

The time has come for us to adopt an attitude of "collective responsibility" for identifying ways to increase access and speed up the approval process that involve agents to treat childhood cancer. The regulatory agencies may need to work outside their defined boxes for this to happen. It is not acceptable to say, well that is not my job, that is not my defined role, that is not what we do. Children with cancer are part of our future. Loosing this valuable resource is a tragedy. This is the perfect opportunity for the FDA to take the lead on this important issue and show the way. I ask that my proposal be seriously considered. I ask this on behalf of Pediatric oncologist around the country, on behalf of their patients and their families.

Thank you.