Patient perspectives: the demand for innovation and safety

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To the credit of the organizers of the Leigh Thompson Renaissance Conference – and the great spirit of the man for whom the conference was named – the central theme was “The patient is waiting.”
http://leighthompsonrenaissanceconference.com/program/

Many thanks to numerous advisors for your ongoing support and valued guidance.

Good morning.
I’d like to start with a brief outline on the role of advocates.
Advocate groups are people closely touched by a disease, such as cancer.
We represent those who suffer the disease and face the limitations of treatment.
We interact with the patient community in order to discover and understand needs.
We communicate about the human costs, … trying to keep the urgency alive,
… which is many times lost when you look at a disease in the abstract.
I’m also dedicating this presentation to the memory of Rick Stimmel and Dan Stephens, lymphoma patients, and valued colleagues, who passed away this year. Rick and Dan both added to our knowledge by participating in clinical trials. Each provided generous support and encouragement to other patients. Their unexpected short survival saddened us, ... And it was also a sobering reminder to all in our group of the danger we face.
I have 3 main reasons for being here:

The first is to review the urgent need for more effective cancer therapies, and to give patient perspectives on aspects of toxicity.

The second is to bring attention to a crisis in clinical research: the stagnation described in the FDA report on The Critical Path.

Finally, I’ll describe how we might improve clinical trial enrollment, and do more efficient research.
In this section I will try to convey the urgency:

The scope of the disease
And aspects of toxicity

"Not everything that counts can be counted; not everything that can be counted counts."

~ Albert Einstein
The data tells us that cancer is everyone’s problem.

Difficult as it may be to realize, … or want to: 1 in 2 men get cancer, and 1 in 3 women.

There are many people with cancer who severely mistrust the medical system; Who will avoid or delay medical treatment, while trying unproven alternatives. This is another aspect of cancer drug toxicity. But everyone gets cancer, including regulators, doctors and drug developers; and their loved ones …

and while the system is not perfect, we counsel that there is no conspiracy -- and to make decisions that are evidence-based.
There are two aspects of toxicity that are well-known to cancer patients. That side effects can contribute to, or cause your death; ... and also narrow your range of treatment choices.

In fact, for lymphomas bone marrow toxicity, leading to infection, might be the leading cause of death. And for indolent lymphomas it seems that we don’t run out of options so much as the ability to tolerate them.
Toxicity leading to “a narrowing range of choices”

“In a sense Billy's no longer at the helm, the conditions are, and all he can do is react. If danger can be seen in terms of a narrowing range of choices, Billy Tyne's choices have just ratcheted down a notch.”

~ The Perfect Storm.

In the Perfect Storm the narrator defines DANGER as a narrowing range of choices. Patients and clinicians call it “burning bridges” When designing clinical trials investigators should be mindful of this aspect of study protocol, for it can have an impact on enrollment.
Unproductive Toxicity

a function of

Not **matching the drug to the patient.**

\[ \ldots \text{when a drug has a 20\% response rate, 80\% suffer} \]
\[ \text{toxicity for no benefit.} \]

Not **accounting for patient differences**

in the biology of the tumor

in immunity

in metabolism, half-life \[ \ldots \]

"The trick with molecular targeting is that you have to be able to \textit{match the drug to the patients}. And until you understand how the drugs work, why they work, and for whom they work, your results might not be as remarkable as you would like for them to be.\]

\[ \text{Once we understand how to match the drug to the patient, I think we will see many, many examples like imatinib \textit{Gleevec}.}^* \text{ ~ Dr. Brian Druker, Howard Hughes Medical Institute} \]

Obviously, toxicity is bad, but what can be worse than **unproductive toxicity** – getting only the side effects of the drug and no benefit \ldots and often significant harm?

Unfortunately, for some cancers this risk is common, and considered better than having no chance at all.

Unproductive toxicity is a function of not accounting for patient differences in the biology of the tumor, or in immunity, or in how the drug is metabolized.

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It was this quote from Dr. Druker, about matching drugs to patients that got many advocates thinking about the necessity for a new approach to clinical research.
Here’s a comment from Mark, a member of our lymphoma support list.

“While I'm grateful for the number of options we have before us, sometimes I wish we didn't have quite so much to analyze and contemplate (and wonder if we got wrong).

Ironic that, at the end of the day, it's still a crap shoot.”

~ Mark F. (Lymphoma survivor)

His words speak to the uncertainty:
  the concerns about toxicity …
  the trial and error aspect of care;
… and the high level of anxiety that this circumstance produces.
On to another aspect of toxicity, unpredictable toxicity, which also relates to patient differences.

I know that some patients treated for lymphoma can suffer painful and irreversible neuropathy, because of how slowly their body clears Vincristine.

Note that the clearance of this drug can vary significantly in children and adults.

2. bcancer.bc.ca
The next section is about evidence of a “clinical research crisis.”

But also, it’s about opportunities for accelerated progress and innovation, if we dare to change the approach.
Evidence of the crisis

What’s Wrong with Our Cancer Models?

“Response rates among unselected cancer patients in phase I studies are seldom more than 10%.” ¹

“Nine of ten attempts to bring a cancer drug to market fail.” ¹

“Very few patients, less than 5% of all available patients, enroll in protocol studies.” ²

1. What’s wrong with our cancer models?

2. The ODAC Chronicles 2005 ~ Antonio J. Grillo-Lopez, MD Chairman, Neoplastic and Autoimmune Diseases Research Institute

On this slide is evidence of the crisis in clinical research, cited by Alexander Kamb and Dr. Grillo Lopez.

Given the low response rates in phase I studies, ...
and that one in ten attempts to bring a cancer drug to market succeed, ...

... we might conclude that the low enrollment in clinical trials indicates good judgment by patients and their treating physicians.
We need each other

• Importance of timely participation
  – delays are costly to sponsors and to patients.

• If patients fail to sign on in adequate numbers ...
  … the assessment of the therapy will not be made
  no matter how well the study is designed from the
  point of view of regulators and scientists.

The urgency of our situation requires that we avoid unnecessary delay,
and that we evaluate new therapies objectively, and efficiently.
Delays are costly to sponsors and to patients.
We [patients] are anxious to help and feel ourselves to be outside the system.
Importantly, if patients fail to sign on to clinical trials in adequate numbers,
… the assessment of the therapy will not be made, no matter how well the
study is designed from the point of view of regulators and scientists.
Here on this slide we have the results of a survey conducted by CancerConsultants.com. It found that 60% of patients (who use the internet) are actively seeking access to clinical trials, but less than 5% participate, overall.

These results indicate that the primary problem with accrual is not the attitudes of patients. I know from my support experience that patients will make great sacrifices to participate in a study – such as travel across the continent – ... if the study is thought to have a potential advantage over standard therapies.
It’s clear to me (for lymphoma at least),
that the gap between what is and what’s possible - in respect to treatment –
has never been wider.
To close the gap we need to test new agents and protocols,
... but the sheer number of new agents is an obstacle,
as each study must compete for patients in the same small pool
- approximately only 5% of the patient population.
Here we have an assessment from the FDA in the publication, referred to as the Critical Path.

I can tell you that this text – coming from this source - is particularly frightening to people who face cancers.

**FDA on the promise of innovation; the evidence of stagnation**

“... the current medical product development path is becoming increasingly challenging, inefficient, and costly.

... the number of new drug and biologic applications submitted to FDA has declined significantly.

... If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical revolution may not deliver on its promise of better health.”

1. *Innovation / Stagnation – Challenge and Opportunity on the Critical Path to New Medical Products ~ FDA (2004)*
And here, despite the promise for innovation by new technologies, we see a significant 10-year downward trend in major drug submissions to the FDA, ... reported by the FDA.

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This table shows response rates for cancer drugs in phase I trials.

My take is that the clinical difference in response means that there’s an underlying difference in the disease, or in the patients.

But if we can identify who the drug is for, there’s a potential to benefit many individuals.

For example: a 2% response in 1.8 million patients with prostate cancer is 42,000 individuals, in the US alone.

Note: that when we develop drugs for molecular subtype of the disease, orphan drug incentives may well apply.
PROPOSALS
for doing efficient clinical research

(1) Make History:
Fund an Essential Resource – the NBN

(2) Work to harmonize research goals with the clinical needs of patients

“When a task is difficult you have to change the approach; you have to create and apply new tools.”

~ Charles Schwartz
I believe there’s an urgent need for a shared resource 
... that can serve the entire industry and academia 
... in order to accelerate discovery and do more efficient research: 
a National Tissue Bank

Some of the main services of the resource will be the standardized 
... capture, storage, and analysis of biospecimens,  
... including tracking of donors to help correlate response to treatment 
to the underlying biology of the tumor and other differences in patients.

But will a highly competitive industry help to fund a cooperative resource?
I predict that once informed, cancer patients will donate the tissue, and gladly.
Advice of FDA: Critical Path

“... develop new, publicly available scientific and technical tools ... that make the development process itself more efficient and effective and more likely to result in safe products that benefit patients.

And ... a knowledge base built ... on reliable insights into the pathway to patients.” ¹

A National Biospecimen Network!
http://www.ndbc.org/about_nbc/reports/pdfs/FINAL_NBN_Blueprint.pdf


Probably, the FDA cannot give specific advice on how to improve predictability and efficiency along the critical path, but there is substantial evidence that a root problem in clinical research is in failing to account for underlying biologic differences among tumors.
I want to emphasize that in order to have confidence in the drugs we use, we ought not lower standards for testing – as recommended by some in the industry, [and some patients as well.]

But we also have to address the enrollment problem in clinical trials - ask why, and make changes accordingly.

One recommendation is to try to make clinical trials more desirable as treatment decisions. It won’t be easy, because there’s often a tension between getting research answers, and optimally meeting the clinical needs of patients.

But larger samples and faster enrollments may compensate for the changes.

And trials that select patients based on biological characteristics of the patient’s tumor, will be more promising to patients, and will reduce the risk of unproductive toxicity.

And if response rates in stratified studies improve as expected, fewer participants will be required to obtain statistically significant results.
Cancer patients will be very careful about treatment decisions. Always.

Each patient has one life to experiment with, and the role of the patient’s physician is to do what is best for their patient; it is not to advance the science, or to help win marketing approval of individual agents.

These are my impressions:

Therapies with low expected toxicity will enroll patients the fastest.
For example, a vaccine study at Stanford for patients with indolent lymphoma - that did not require chemotherapy – achieved 100% enrollment in about a week.

Obviously, patients with high-risk disease need potentially curative protocols that sequence and combine complementary therapies.

Patients seeking to manage lower risk disease will not be interested in trying new single agents, unless they are targeted, immune-based, expected to be low toxic, and not likely to burn treatment bridges.

Providing incentives to treating physicians and seeking better ways to recruit patients – remedies often proposed by different parties – will not fix an underlying problem: the appeal of the clinical trial to the patient as a treatment decision.
In summary, cancer will affect virtually every family, and therefore discovery of better treatments must be a national priority.

Treatment resulting in unproductive toxicity – side effects with no benefit – is worst of all.

The toxicity of cancer drugs can cause death and often narrow the range of treatment choices.

Unproductive toxicity is a function of not matching the drug to the patient.

Toxicity cannot always be predicted, which contributes to the trial and error aspect of care, and causes distress.

The clinical research crisis calls for a new approach.

We should all be fearful that the industry will give up if current trends continue.

The poor enrollment in clinical trials both reflects on, and contributes to, the research crisis.
Finally, the evidence is telling us that we need a better approach to cancer research:
A new infrastructure to provide standardized
... capture, storage, analysis, and shared access of Biospecimen data.
This will enable a targeted approach based on differences in the biology of tumors and the patient.
It will also accelerate stratified clinical research to better match the drug to the patient in order to reduce toxicity and improve survival.
And poor enrollment in clinical trials is telling us:
that we need to better harmonize research goals with the clinical needs of patients.
... [that the patient’s disease-related necessities and clinical goals should become a major focus in protocol design ... for both practical and ethical reasons.] *

* Inserted after talk. Not said, but described in conversations.
The end.

Thank you for listening.
It's appreciated.