

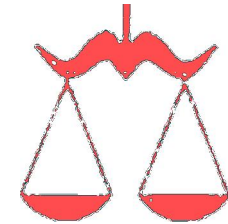
Close Calls

Perspectives, Preparations and Participation on FDA Advisory Committees

2008 Patient Representatives FDA Workshop

Karl Schwartz

President, Patients Against Lymphoma
Patient Representative ODAC, Patient Consultant



Caregiver to spouse,
twelve year survivor of follicular lymphoma

The views expressed are from independent work and do not represent the policy or perspectives of organizations to which the author is associated.



Outline

Part I) A few Perspectives:

- Open mind | Conversations on evidence
| Understanding and providing the context

Part II) Advisory Committee Preparations (*Long*):

- Getting ready | Nerves
- The indication: a common serious complication of cancers and cancer treatment
- Sponsor's rationale
- Key issues, concepts, terms

Part III) Advisory Meeting Participation (*Intense*)

- What happened

Perspective: keeping an open mind

- Because of the daunting complexity of human and disease biology ... all drug effects cannot be anticipated, measured, or readily accounted for.
- The data you are reviewing is likely the most complete and comprehensive that's available for this drug for this indication.

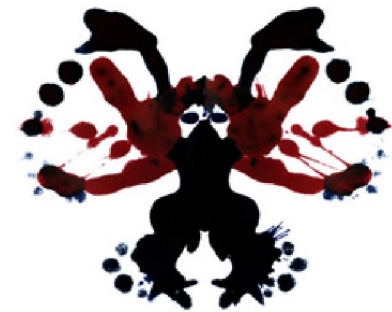
*“In theory there is no difference between theory and practice. ... in practice there is.”
~ Yogi Berra*



Begin Part I

Perspective: Our role in fostering community understanding of the process

- Testimonials? (*no detail, no denominator...*)
- Observational studies? (*small / no control / many sources of bias*)
- Risk / benefit - tradeoffs | net benefit?
- Are we measuring the right things?
(*surrogate / survival*): “*Events averted or lives improved?*¹”
- Awareness of bias: types and sources
(*sponsor / investigator / patient / study method*)
- Wishful thinking?



*Consider the confusion and danger ...
if the approval of drugs were based on opinion and theory?*

1) Redefining Quality—Implications of Recent Clinical Trials, Harlan M. Krumholz, M.D., and Thomas H. Lee, M.D.

Perspective: the human context

- **The indication** ... natural history
 - Short or long survival?
 - Devastating? ... debilitating? ... manageable?

- **Available therapies?**
 - Effective? Curative? Improve survival?
 - Impacts: Quality of life? Toxic? Risks?
Reversible or permanent toxicity?
Short- or long-term side effects / risks?
 - Does it preclude use of other interventions?

Perspective: *What's acceptable as risk or even a surrogate endpoint depends on the **indication** and also what's **available as therapy** – the context*

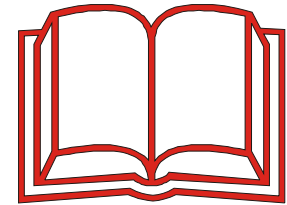


Remembering Denise Stafford

51 years old
Dx: 10/03;
Deceased: 3/06
6 R-CHOP + 2 R-CVP - PR
9/04 4 x R - PR
10/04 RICE x 3
1/05 ESHAP x 2
6/05 Fludara + R + Doxil
7/05 2nd treatment -
continued improvement
8/05 3rd treatment - 3rd time
the charm?

ADVISORY COMMITTEE PREPARATIONS *(Long)*

- Allow sufficient time
 - Materials can be considerable and technical
 - Use outside medical resources, if needed
 - Ask for help, if needed | Maintain confidentiality
 - You will be asked to vote; provide reason for your vote
- Understand the context, indication & rationale
- Identify key questions
 - Why is this before the Advisory committee?
- Prepare concise questions / comments; prepare to drop if already addressed



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-
-
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Confidential!

Part II

Nerves

- Prepare
- It's not about me
- We are experts:
provide human context!
- Have concise narratives ready
 - Be flexible
 - Provide *unique* patient perspective:
represent recipient of intervention
- Also “*know what we don't know.*”
 - Acknowledge limitations of scientific background
when raising technical issues – phrase as question



context: VTE (clotting) and cancer

- association well established,
- limited understanding of pathophysiology
- known to be multifactorial:
 - tumor-related mechanisms:
 - release of pro-coagulants by tumor cells or macrophages-tissue factor
 - patient-related risk factors
 - advanced age, surgery, periods of immobilization, infections)
 - anti-cancer treatment-related thrombogenic effects
 - chemotherapy, endocrine treatments and
 - other anti-cancer therapies
 - vascular catheters

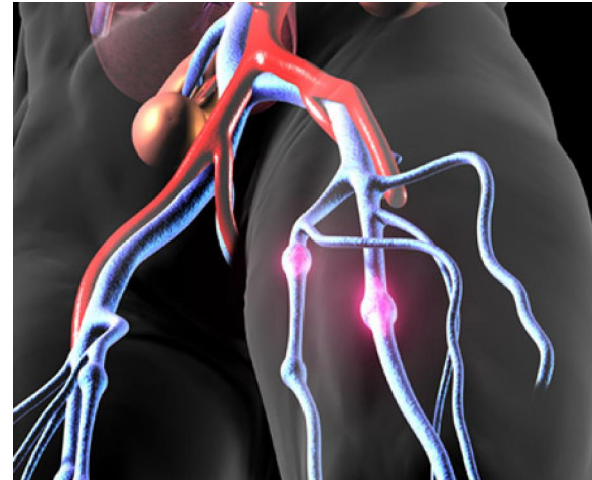


Image: clevelandclinicmeded.com



Annual incidence / prevalence of *deep vein thrombosis* DVT

- **Incidence**: first episode in general population = 117 / 100,000
- **Prevalence**: first episodes in general US population = > 200,000
- **Cancer** diagnoses increases risk: **four** to **sevenfold**
- **Chemotherapy** increases risk **sixfold**

Fragmin features

- Low molecular weight heparin
first marketed in Germany, 1985;
approved in US, 1994
 - For the prevention of deep vein thrombosis (DVT),
which may lead to pulmonary embolism (PE)
 - Also for prevention of ischemic (stroke) complications

KEY ADMINISTRATION FEATURES:

- Administered *once* daily, subcutaneously
- Does *not* require ability of patient to swallow
- Monitoring anticoagulant effects in blood *not* required



Fragmin: Sponsor's rationale

New indication

Fragmin already approved for similar use.



Sponsor's rationale:

- High risk of recurrence of VTE in cancer patients
- CLOT study shows:
 - Fragmin (injection) reduced recurrence of these events and has a favorable risk/benefit profile compared to Oral Anticoagulant (OAC).

<http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4235B1-03-01PfizerInc-background.pdf>

Historical basis for selection of primary endpoint: **recurrence of VTE**

Reported VTE recurrence rates:

<u>With</u> cancer	<u>Without</u> Cancer:
20.7%* Prandoni (2002) 842 (181 with cancer)	6.8%*
8.5%* Merli (2001) 900 (141 with cancer)	3.8%**
8.6%** The Columbus Investigators (1997) 1021 (232 with cancer)	4.1%**

*** 12 month recurrence rate ** 3 month recurrence rate**



Some key definitions & concepts

- **Venous thromboembolism (VTE) includes:**
 - **Deep Vein Thrombosis (DVT)** – formation of clot
 - **Pulmonary Embolism (PE)** – clot that migrates to artery in lung
 - **Fragmin** (Dalteparin – study drug) low weight molecular heparin
 - **Oral AntiCoagulant therapy (OAC)** – active control
-

- **Competing risk**

if the patient dies in study, they cannot have a VTE event

- **On-treatment Mortality** in this study there was narrow time frame for definition, which led to:

- **Informative Censoring** “When those lost to follow-up have different probability of outcome than those who remain”

See Epidemiologic Methods (outside source)



endpoints in this study

Are we measuring the right things?

The **primary endpoint and objective:**

- Compare Fragmin to Oral Anticoagulant: prevent recurrence of VTE in cancer patients with acute, symptomatic, proximal lower limb deep vein thrombosis (DVT), pulmonary embolism (PE) or both.

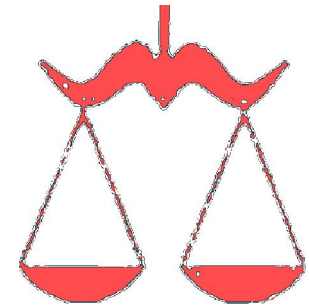
Secondary Objectives compare treatment groups:

- Reduce risk of symptomatic DVT, or PE, or central venous thrombosis of the upper limb(s), neck, or chest (Central Venous Thrombosis [CVT])

Secondary Endpoints

- Composite: first occurrence of symptomatic, and objectively documented lower limb DVT, or PE, or CVT during the 6-month study period
- **Survival** over 6 and 12 months?
- Major bleeding events during the treatment period.
- Any major and minor bleedings during the treatment period.
- Type, incidence, severity, relatedness of adverse events; abnormalities in blood chemistry.
- QOL during the treatment period

Some other factors to weigh



- **Patient Characteristics at Baseline:**
 - **Example: Were risk profiles balanced in each arm?**
- **Mortality During 6-Month Treatment Period?**
- **Mortality During 12-Month Post-Randomization Period?**
- **Reasons for Discontinuation of Study Medication in As-Treated Population?**
- **Comparing major bleeding events? | Any bleed events?**

Objective test?

the MEETING DELIBERATION

(Intense)

- Arbitration of a close call
- Feels like a legal proceeding
- Sponsor makes it's case
 - Having had opportunity to review FDA concerns (briefing doc)
- FDA review team cites concerns
- Committee asks questions of each side
- You vote on specific questions; may be asked to provide the reason.



Part III

study design issues

- Each arm used investigational agent (Fragmin)
 - Control arm used Fragmin for short period at beginning of treatment (**confounding?**)
- Open label (not blinded)
 - Investigators and patients knew which drug they were receiving
 - **Did this introduce bias?** – earlier reporting or detection of primary and secondary events in one study arm or other?
- On-treatment mortality was high in Fragmin group, and also in control group, but during use of Fragmin.
 - **Signal?** Unrecognized adverse mechanism of Fragmin?
 - ... or explained by *informative censoring*?
- Blood tests needed to test for coagulation factors in control (OAC) group
Did this introduce bias? ... how easy it is to detect VTE?





Signal? | Survival?

- Was higher on-treatment mortality from cancer due to an **unrecognized adverse drug effect**?

... **Does Fragmin increase risk of death from the cancer?**

Cited published hypothesis:

*“... the events responsible for thrombosis in cancer appears to be a result of an over exuberant host response in an attempt to delimit tumor growth.”**

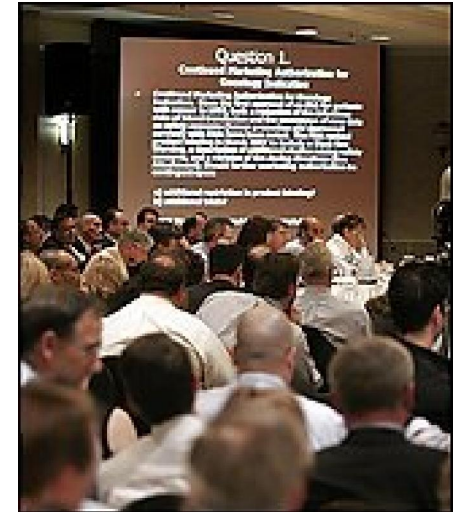
- If VTE leads to mortality in cancer patients, why did we *not* see an improvement in **survival** in the Fragmin arm of the study?

* **Molecular basis for the relationship between thrombosis and cancer.** [Rickles FR, Falanga A.](#)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11516455&dopt=Abstract

the MEETING final vote

- Package provided before meeting should contain questions (*make sure you have this part!*)
 - Questions also displayed on monitor for benefit of observers
- The Chairperson asked for explanation to accompany our votes
- You can ask Chair for clarifications before voting ... you can abstain on any question.
- **A decisive factor:** Informative censoring judged good explanation for high on-treatment mortality
- **Fragmin approved for indication**



Thanks for listening!