Clinical Trials or Standard Treatment?
Understanding Options for Blood Cancers

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Welcome and Introductions

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Understanding Options for Blood Cancers

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March 18, 2015

Disclosures

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- Consulting
  - Celgene Corporation
  - Genentech, Inc.
  - Gilead Sciences, Inc.
  - Pharmacylics, Inc.
  - Seattle Genetics, Inc.
  - Spectrum Pharmaceuticals, Inc.

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How a Drug is Developed for Blood Cancers

- Preclinical rationale – laboratory studies
- Pharmacology and manufacturing
- Animal studies – toxicity and efficacy
- **Human studies**
  - **Phase I**
  - **Phase II**
  - **Phase III**
  - **Phase IV**

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Blood Cancer Drug Development: Unique Challenges

- Many different diseases
  - Treatment approaches vary from observation to bone marrow transplantation
- Why do we need new treatments?
  - Increase the cure rate
  - Improve survival
  - Minimize toxicity/side effects
- Relatively rare diseases
  - Requires multicenter or even international collaborations
- Many existing agents have significant activity

Cost of developing a drug may exceed several hundred million $

Increasing interest in "small diseases" as progress can be made

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Phase I Trials

- History
  - First in human
  - Goal: define maximum tolerated dose of potentially active agents
  - PRIMARY ENDPOINT: TOXICITY
  - Generally single-arm studies in patients with refractory disease
  - Often around 20 patients
- Blood cancer issues
  - Uncommon for first-in-human studies to be done in blood cancers
  - "Disease-specific" phase I more common
  - Novel biological agents require new trial designs
    - "Biologically active" dose more appropriate than maximum tolerated dose
  - Primary endpoint: remains toxicity

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Phase II Trials

- Very common in oncology
  - May study a variety of doses and schedules
  - Goal: determine activity in disease
  - PRIMARY ENDPOINT: EFFICACY
  - Common to have many correlative scientific studies
  - Often single-arm studies in patients with either newly diagnosed or refractory disease
  - Usually between 20 and 80 patients
- Randomized phase II
  - Becoming more common
  - Necessary when "historical control" group does not exist
  - May explore different agents or combinations to determine optimal regimens for the ultimate phase III trial
  - Primary endpoint: efficacy, but two arms not directly compared

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Phase III Trials

- Randomized trials to definitively evaluate efficacy
  - Single dose and schedule, determined by phase II
  - Large (>100 patients) with substantial statistical power
  - PRIMARY ENDPOINT: EFFICACY
  - Very few correlative scientific studies
- Placebo rarely utilized in oncology
  - Standard of care generally is control arm
  - Numerous examples in lymphoma of importance of randomized phase III trials
  - FDA may allow a single-arm trial if there is no clear standard of care (relevant particularly to rare diseases)

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FDA, US Food and Drug Administration.

Lessons in Blood Cancers From Phase III Trials

- CHOP is the standard for aggressive NHL
  - High priority lymphoma study
  - CHOP vs MACOP-B vs m-BACOD vs ProMACE-CytaBOM
  - Equivalent outcomes except for toxicity
- ABVD is the standard for advanced stage Hodgkin lymphoma
- Abbreviated CHOP with radiation is sufficient for localized aggressive NHL
  - CHOP x 3 + XRT vs CHOP x 8
  - Superior outcomes in combined modality arms

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; **CHOP**, cyclophosphamide, doxorubicin, vincristine, prednisone; **MACOP-B**, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; **m-BACOD**, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone, methotrexate, leucovorin; NHL, non-Hodgkin lymphoma; **ProMACE-CytaBOM**, cyclophosphamide, doxorubicin, etoposide cytarabine, bleomycin, vincristine, methotrexate and prednisone; **XRT**, radiotherapy.

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Lessons in Oncology From Phase III Trials

- Role of high-dose chemotherapy and autologous stem cell support in high-risk breast cancer

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R-CHOP for DLBCL

Summary of 4 large randomized trials

- R-CHOP produced a statistically and clinically meaningful improvement in remission and survival compared with CHOP
- Benefit seen in all age groups and all risks of NHL. Low-risk patients may experience the most benefit
- No role for "maintenance" rituximab following chemotherapy if R-CHOP is given initially

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R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

Recent US Phase III Trials in Lymphoma

- Hodgkin lymphoma
  - ABVD vs Stanford V
- Aggressive lymphoma
  - EPOCH-R vs CHOP-R
  - Early vs late ASCT
- Follicular lymphoma
  - RESORT trial
  - R-CHOP vs CHOP + I-131 tositumomab
  - Idiotype vaccine (placebo)

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; **ASCT**, autologous stem cell transplant; **CHOP**, cyclophosphamide, doxorubicin, vincristine, prednisone **EPOCH-R**, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; **R-CHOP**, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone. 12

Phase IV Trials

- "Post-marketing" trials
  - Larger patient groups to determine additional toxicity profile (required by FDA for approval)
  - New indications
  - New schedules
  - New routes of administration

FDA, US Food and Drug Administration.

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Correlative Laboratory Projects

- Tumor and serum "banks"
  - Growing in importance
  - New regulations require extensive consenting
  - Importance in evaluating "targeted therapy"

As important for the future of blood cancer research as participating in large clinical trials

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Who Conducts Clinical Trials?

- Sponsor (organizer)
  - National Cancer Institute
  - Cooperative groups (CALGB/Alliance, SWOG, ECOG)
  - Pharmaceutical companies
  - Groups of academic and treatment centers
  - Individual academic and treatment centers
- Investigator (local center)
  - Academic centers/medical colleges
  - Large hospitals
  - Small hospitals and clinics
  - Small clinical practices
- Virtually all "blood cancer expert" MDs are doing trials

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Advantages to Research

- Access to novel agents
- "Cutting-edge" care
- Standardization of staging and follow-up
- Team approach to care
  - Dedicated trials nurse; data manager; other MDs
  - Attention to details
- Altruism
- Reasonable expectations
  - Full understanding of rationale and goals of trial
  - Reassurance that you can leave trial if new information becomes available
  - Results of clinical research
    - Patience….

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Myths About Clinical Research

- All clinical research is performed at large academic medical centers
- Use of placebo and deviation from standard care
- Clinical research increases the cost of care
- All treatments on clinical trials are free

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Cancer Clinical Trials

- Approximately 1–2% of patients overall enroll in clinical trials
- NCI cooperative group clinical trials from 1998–1999
  - 35% of subjects 60 or older
  - 17% of subjects 70 or older

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NCI, National Cancer Institute.

Why Don't Patients Enroll in Clinical Trials?

- Possibilities
  - Lack of awareness (patient and MD)
  - Nature of treatment
  - Feeling that they are not end stage and don't need trial
  - Fear of unproven treatments
  - Excluded by comorbid illnesses
  - Complexities of study design and need for procedures
  - Concern about perception of benefit
  - Insufficient financial, logistic, social support
  - Distance
  - MD financial incentives/disincentives

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Slow Accrual To Cancer Clinical Trials Causes Patients To Die Unnecessarily

- US national CHOP vs CHOP-R study in DLBCL
  - 600 patients, accrued nationally over 3 years
  - To complete 1 year earlier, would have needed 100 more patients/year nationally
  - Amounts to about 1–2 patients/per center
- 20% improvement in cure rates
  - During 1 year, 20,000 DLBCL pts diagnosed in US
  - Completing study 1 year earlier would have saved estimated 4000 lives

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; **CHOP-R**, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **DLBCL**, diffuse large B-cell lymphoma.

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Is a Clinical Trial Right for You?

- Ask your doctor
  - Do they participate?
  - If not, can they refer you to someone who does to discuss?
  - Most blood cancer expert centers are involved
- Reach out
  - LLS (www.LLS.org), other organizations
  - Internet/clinicaltrials.gov
  - Company websites
- Clinical trials should be at least considered for every situation

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Question & Answer Session

The speaker's slides are available for download at www.LLS.org/programs

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The Leukemia & Lymphoma Society (LLS) offers:

• Live, weekly Online Chats are moderated by an oncology social worker and provide a friendly forum to share experiences.

- **WEBSITE: www.LLS.org/chat**

• Co-Pay Assistance Program offers financial assistance to qualified cancer patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE: www.LLS.org/copay**
- **TOLL-FREE PHONE: (877) LLS-COPAY**

• For more information about blood cancers and other LLS programs, please contact an LLS Information Specialist.

- **EMAIL: infocenter@LLS.org**
- **TOLL-FREE PHONE: (800) 955-4572**

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