Clinical Trials: Registration, Results Reporting, and Data Sharing

Jerry Sheehan
Assistant Director for Policy Development
National Library of Medicine – National Institutes of Health

OECD Expert Workshop on Knowledge Markets in Life Sciences
16-17 October 2008, Washington, DC
Overview

- Transparency of clinical trials information
  - Motivations
  - Policies
- ClinicalTrials.gov
  - Registry
  - Results database
- Integration with broader biomedical information infrastructure

*Perspective of a national library/information center*
National Library of Medicine

More than a (just) a Library

- World’s largest medical library (>8 million artifacts)
- Intramural research laboratories
  - National Center for Biotechnology Information
- Extramural research and training
- Information services for various audiences
  - Medline – citations to published literature
  - PubMed Central – full text journal articles
  - MedlinePlus – consumer-oriented information
  - Special Populations - Arctic Health, Native American, Asian American, Seniors
  - Genbank – gene sequences
  - Genetics Home Reference
  - dbGaP – genome wide associations
  - PubChem – small molecules database
  - Hazardous Substances Database
  - ToxTown - for school children
  - ClinicalTrials.gov

www.nlm.nih.gov
Increasing the transparency of clinical trials information

Motivations
• Science – Communication of research objectives and results; Enhance recruitment
• Medical care – trials inform medical decision-making
• Ethics – Human volunteers involved
• Safety – IRBs can better evaluate risks/benefits

Concerns about transparency:
Drug safety

Report: Vioxx linked to thousands of deaths
Newspaper cites government study on recalled pain drug

MSNBC staff and news service reports
Updated: 6:15 p.m. ET Oct. 6, 2004

Merck & Co.’s arthritis drug Vioxx may have led to more than 27,000 heart attacks and sudden cardiac deaths before it was pulled from the market last week, the Wall Street Journal reported Wednesday, citing an unreleased study by government regulators.

June 2, 2004

New York Sues Maker of Antidepressant Drug Paxil

By KENNETH N. GILPIN

The New York State attorney general accused the British drug giant GlaxoSmithKline of consumer fraud today, asserting that the company had withheld negative information and misrepresented data about the efficacy and safety of prescribing the antidepressant drug Paxil to children.
Concerns about transparency: Public trust

Clinical Trials and Public Trust

In July, hope was expressed on this page about new developments in the accessibility of clinical trial data. Several leading medical journals had pressed for a requirement that all clinical trials be placed in a public registry, a proposal endorsed by the American Association of Physicians (AMA) and the Association of American Medical Colleges. The AMA had urged the institutional review boards (IRBs) that review trial protocols to require such registration before approval of a drug. The World Health Organization further supports an international registry.

That good news has proved transitory, as subsequent events have damaged the public’s faith in a process that is, after all, vital to its health. The alleged falsely elevated risks associated with its blockbuster pain drug, with changes that the company knew of, that scandal followed another: a year-long del Administration (FDA) to warn about the suicide given to children.

What’s needed to restore confidence in the system is to focus blame on the companies, not on their prices. Although clinical trials that sponsor and organize them want the “right” res, abund. An important trial may involve many centerovershared members. One resistant IRB can be the others have approved. Many trials are outsourced research organizations (CROs), which are motivated not the wedding coordinator wants to please the

Impugning the Integrity of Medical Science
The Adverse Effects of Industry Influence

The profession of medicine, in every aspect—clinical, education, and research—has been inundated with profound influence from pharmaceutical and medical device industries. This has occurred because physicians have allowed it to happen, and it is time to stop.

Two articles in this issue of JAMA provide a glimpse of one company’s apparent misrepresentation of research data and its manipulation of clinical research articles and clinical reviews; such information and articles influence the education and clinical practice of physicians and other health professionals. The direct influence of for-profit companies on education and clinical practice has been well documented, so this Editorial deals primarily with clinical research.

Catherine D. DeAngelis, MD, MPH
Phil B. Fontanarosa, MD, MBA

It is clear that at least some of the authors played little direct roles in the study or review, yet still allowed themselves to be named as authors. Individuals, particularly physicians, who allow themselves to be used in this way, especially for financial gain, manifest a behavior that is unprofessional and demeaning to the medical profession and to scientific research.

The study by Popay and Kronmal, which is based on analysis of published articles, information provided by the company to the US Food and Drug Administration (FDA), and
Concerns about transparency: Congressional interest

NEWS RELEASE

Committee on Energy and Commerce
Rep. John D. Dingell, Chairman

For Immediate Release: January 22, 2008
Contact: Jodi Seth or Brin Frazier, 202-225-5735

Dingell, Stupak Continue ENHANCE Trial Inquiry

Question Merck, Schering-Plough on Advisory
Board and Employee Stock Sales
Request Information, Records from CMS
FDA Amendments Act of 2007
§801--Expanded Clinical Trial Registry Data Bank

• **Within 90-Days of Enactment (12/26/07)**
  – Expand existing clinical trials registry to accept broader scope of trials, more required information
  – Registration requirements for “Responsible Parties” (new and updated registrations for serious & life-threatening conditions)
  – Link from registry to specified FDA & NIH results information

• **Within 1 Year of Enactment (9/27/08)**
  – Deadline for registering ongoing trials that are not for serious or life-threatening conditions
  – Basic results database and results reporting

• **Future Enhancements (9/27/2008 +)**
  – Adverse event reporting (18-24 months)
  – Pilot Quality Control study to inform rulemaking
  – Rulemaking for Expanded Registry and Results Database (3 yrs)

• **Penalties for non-compliance**
  – Withhold Federal grant funding
  – Monetary fines
ClinicalTrials.gov

- World’s largest trials registry
  - 60,000+ trials as of September 2008
  - 350-400 new trials registered WEEKLY
  - From all 50 US States + 150 countries
- Established in 2000
  - Mandated by FDA Modernization Act of 1997
  - Required for trials of drugs for serious & life threatening conditions
- Continually expanded and modified to accommodate other registration policies
  - ICMJE policy
  - WHO Registration Data Elements
- Accepts registration of trials of wide range of medical interventions across the globe

Undergoing significant transformation in response to FDA Amendments Act of 2007
# Clinical Trials Registries

Number of trials registered as of 15 Sept 2008

<table>
<thead>
<tr>
<th>Registry</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClinicalTrials.gov</td>
<td>61,665</td>
</tr>
<tr>
<td>ISRCTN (UK)</td>
<td>7,110</td>
</tr>
<tr>
<td>Australian New Zealand Clinical Trial Registry (ANZCTR)</td>
<td>2,402</td>
</tr>
<tr>
<td>Netherlands Trial Registry</td>
<td>1,343</td>
</tr>
<tr>
<td>Chinese Clinical Trial Register (ChiCTR)</td>
<td>95</td>
</tr>
<tr>
<td>Clinical Trials Registry – India (CTRI)</td>
<td>93</td>
</tr>
<tr>
<td>Sri Lanka Clinical Trials Registry</td>
<td>31</td>
</tr>
</tbody>
</table>
New Trial Registrations at ClinicalTrials.gov

- 250 new trials/week
- 800 updates/week
- 375 new trials/week
- 1300 updates/week
Types of Trials Registered at Clinical Trials.gov

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventional</td>
<td>51,982</td>
<td>84%</td>
</tr>
<tr>
<td>-- Drug &amp; biologic</td>
<td>39,182</td>
<td>64%</td>
</tr>
<tr>
<td>-- Device</td>
<td>3,342</td>
<td>5%</td>
</tr>
<tr>
<td>-- Surgical procedure</td>
<td>8,032</td>
<td>13%</td>
</tr>
<tr>
<td>-- Behavior, gene therapy, other</td>
<td>6,921</td>
<td>11%</td>
</tr>
<tr>
<td>Observational</td>
<td>9,577</td>
<td>16%</td>
</tr>
<tr>
<td>Undefined</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>“Applicable clinical trials”</td>
<td>10,477</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>61,665</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

As of 15 September 2008
Wide Range of Registrants at ClinicalTrials.gov

### Trials by Data Provider

<table>
<thead>
<tr>
<th>Trials by Data Provider</th>
<th>No. Records</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>University, Other</td>
<td>25,461</td>
<td>41%</td>
</tr>
<tr>
<td>Industry</td>
<td>18,624</td>
<td>30%</td>
</tr>
<tr>
<td>NIH and other Federal</td>
<td>17,580</td>
<td>29%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>61,665</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

As of 15 September 2008

### Trials by Location

<table>
<thead>
<tr>
<th>Trials by Location</th>
<th>No. Records</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>US only</td>
<td>30,247</td>
<td>50%</td>
</tr>
<tr>
<td>Non-US only</td>
<td>20,487</td>
<td>33%</td>
</tr>
<tr>
<td>Both US &amp; Non-US</td>
<td>4,592</td>
<td>7%</td>
</tr>
<tr>
<td>Unknown</td>
<td>6,339</td>
<td>10%</td>
</tr>
</tbody>
</table>

As of 15 September 2008
FDAAA Registration Requirements

• Must register Applicable Clinical Trials
  – Drugs, Biologics and Devices
  – Excludes Phase 1 studies, feasibility studies
• Voluntary registration accepted
• Registration required 21 days after enrollment of 1st patient
• Required updates (at least annually, more for some elements)
• Post information within 30 days of receipt
• EXCEPT delay posting of information for trials of uncleared/unapproved devices
<table>
<thead>
<tr>
<th>Descriptive</th>
<th>Recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Brief title &amp; summary</td>
<td>• Eligibility criteria</td>
</tr>
<tr>
<td>• Primary purpose</td>
<td>• Gender, age limits</td>
</tr>
<tr>
<td>• Study type</td>
<td>• Healthy volunteers?</td>
</tr>
<tr>
<td>• Primary disease/condition</td>
<td>• Recruitment status</td>
</tr>
<tr>
<td>• Start &amp; completion dates</td>
<td>• Expanded access?</td>
</tr>
<tr>
<td>• Target # of subjects</td>
<td></td>
</tr>
<tr>
<td>• Outcomes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location and contact info</th>
<th>Administrative information</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Name of sponsor</td>
<td>• Unique protocol ID</td>
</tr>
<tr>
<td>• Responsible party</td>
<td>• Other protocol ID</td>
</tr>
<tr>
<td>• Facility name and contact</td>
<td>• IND/IDE protocol ID</td>
</tr>
</tbody>
</table>
Basic Results Reporting: General Requirements

- Applies to results of “applicable clinical trials” of FDA-approved/cleared medical products
- Deadline for submission (in general) within 12 months of the earlier of estimated or actual trial completion date
- Delayed submission with certification
  - Initial approval/clearance: within 30 days of decision
  - New use: within 30 days of FDA action or withdrawal without resubmission for 210 days. 2-year maximum.
  - Extensions for good cause
Basic Results Reporting: Information Requirements

• Demographic & baseline characteristics
  – Table of values, overall and for each arm
  – # of patients dropped out & excluded from analysis

• Primary and secondary outcomes
  – Table of values for each primary & secondary outcome measure, by arm
  – Scientifically appropriate tests of statistical significance

• Point of contact (for scientific information)

• Certain agreements (restrictions on PI to discuss or publish results after trial completion date)
Adverse Events - Default

• Take effect if the Secretary fails to issue regulations within 24 months after the date of enactment [September 2009]

• Serious Adverse Events
  – Table of anticipated and unanticipated serious adverse events
  – Grouped by organ system
  – Number and frequency of event in each arm of clinical trial

• Frequent Adverse Events
  – Table of anticipated and unanticipated adverse events
  – Exceed a frequency of 5 percent within any arm of clinical trial
  – Grouped by organ system
  – Number and frequency of event in each arm of clinical trial
Underlying Philosophy for Results Reporting System

"Make everything as simple as possible..."
…but not simpler.”

Albert Einstein
Bimatoprost 0.03% Versus Travoprost 0.004% in Patients Currently on Latanoprost 0.005%

This study has been completed.

<table>
<thead>
<tr>
<th>Sponsored by</th>
<th>Allergan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information provided by</td>
<td>Allergan</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00440011</td>
</tr>
</tbody>
</table>

**Purpose**

Patients with glaucoma or ocular hypertension currently being treated with latanoprost 0.005%, and in need of additional IOP lowering, will be randomized to receive either bimatoprost 0.03% or travoprost 0.004% in place of latanoprost 0.005%

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma</td>
<td>Drug: bimatoprost 0.05% eye drops</td>
<td></td>
</tr>
<tr>
<td>Ocular Hypertension</td>
<td>Drug: travoprost 0.004% eye drops</td>
<td></td>
</tr>
</tbody>
</table>

**Genetics Home Reference related topics:** early-onset glaucoma

**MedlinePlus related topics:** Glaucoma, High Blood Pressure

**ChemiDplus related topics:** Latanoprost, Tetrahydrozoline, Tetrahydrozoline hydrochloride, Travoprost, Bimatoprost

**U.S. FDA Resources**
Bimatoprost 0.03% Versus Travoprost 0.004% in Patients Currently on Latanoprost 0.005%

This study has been completed.

Study NCT00440011. Last updated on October 7, 2008. Information provided by Allergan

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Interventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design:</td>
<td>Randomized, Single Blind (Investigator), Active Control, Parallel Assignment</td>
</tr>
<tr>
<td>Conditions:</td>
<td>Glaucoma, Ocular Hypertension</td>
</tr>
<tr>
<td>Interventions:</td>
<td>Drug: bimatoprost 0.03% eye drops, Drug: travoprost 0.004% eye drops</td>
</tr>
</tbody>
</table>
# Results: Patient Flow

## Recruitment Details

**Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations**

No text entered.

## Pre-Assignment Details

**Significant events and approaches for the overall study following participant enrollment, but prior to group assignment**

No text entered.

## Reporting Groups

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bimatoprost 0.03% 1 drop nightly for 3 months</td>
</tr>
<tr>
<td>Travoprost 0.004% 1 drop nightly for 3 months</td>
</tr>
</tbody>
</table>

## Participant Flow: Overall Study

<table>
<thead>
<tr>
<th></th>
<th>Bimatoprost</th>
<th>Travoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARTED</td>
<td>131</td>
<td>135</td>
</tr>
<tr>
<td>COMPLETED</td>
<td>127</td>
<td>132</td>
</tr>
<tr>
<td>NOT COMPLETED</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Protocol Violation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawal by Subject</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
## Results: Baseline Characteristics

### Reporting Groups

| Description                                      |  
|--------------------------------------------------|--------------------------------------------------|
| **Bimatoprost**                                  | bimatoprost 0.03% 1 drop nightly for 3 months   |
| **Travoprost**                                   | travoprost 0.004% 1 drop nightly for 3 months   |
| **Total**                                        | No text entered.                                 |

### Baseline Measures

<table>
<thead>
<tr>
<th>Number of Participants [units: participants]</th>
<th>Bimatoprost</th>
<th>Travoprost</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>131</td>
<td>135</td>
<td>266</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age [units: years] Mean ± Standard Deviation</th>
<th>Bimatoprost</th>
<th>Travoprost</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>63.4 ± 12.3</td>
<td>62.7 ± 12.4</td>
<td>63.0 ± 12.3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender [units: participants]</th>
<th>Bimatoprost</th>
<th>Travoprost</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>81</td>
<td>66</td>
<td>147</td>
</tr>
<tr>
<td>Male</td>
<td>50</td>
<td>69</td>
<td>119</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region of Enrollment [units: participants]</th>
<th>Bimatoprost</th>
<th>Travoprost</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>131</td>
<td>135</td>
<td>266</td>
</tr>
</tbody>
</table>
Results: Primary Outcome Measures

<table>
<thead>
<tr>
<th>Primary Outcome Measure: Intraocular Pressure (IOP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure Type</td>
</tr>
<tr>
<td>Measure Name</td>
</tr>
<tr>
<td>Measure Description</td>
</tr>
<tr>
<td>Time Frame</td>
</tr>
<tr>
<td>Safety Issue</td>
</tr>
</tbody>
</table>

### Reporting Groups

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bimatoprost</strong></td>
</tr>
<tr>
<td>bimatoprost 0.03% 1 drop nightly for 3 months</td>
</tr>
<tr>
<td><strong>Travoprost</strong></td>
</tr>
<tr>
<td>travoprost 0.004% 1 drop nightly for 3 months</td>
</tr>
</tbody>
</table>

### Measured Values

<table>
<thead>
<tr>
<th>Measure</th>
<th>Bimatoprost</th>
<th>Travoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants</td>
<td>127</td>
<td>132</td>
</tr>
<tr>
<td>[units: participants]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraocular Pressure (IOP)</td>
<td>17 ± 3.1</td>
<td>17.5 ± 2.6</td>
</tr>
<tr>
<td>[units: mm Hg]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± Standard Deviation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Statistical Analysis 1 for Intraocular Pressure (IOP)

<table>
<thead>
<tr>
<th>Groups</th>
<th>All groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>P Value</td>
<td>0.024</td>
</tr>
</tbody>
</table>
INTEGRATION INTO LARGER BIOMEDICAL INFORMATION INFRASTRUCTURE
Combination Chemotherapy in Treating Patients With Burkitt’s Lymphoma or Burkitt’s Leukemia

This study is ongoing, but not recruiting participants.

Sponsored by: Medical Research Council
Information provided by: National Cancer Institute (NCI)
ClinicalTrials.gov identifier: NCT00040690

Purpose

RATIONALE: Drugs used in chemotherapy use different ways to stop cancer cells from dividing so they stop growing or die. Combining more than one drug may kill more tumor cells.

PURPOSE: Phase II trial to study the effectiveness of combination chemotherapy in treating patients who have Burkitt’s lymphoma or Burkitt’s leukemia.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia Lymphoma</td>
<td>Drug cyclophosphamide</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Drug cytarabine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug doxorubicin hydrochloride</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug etoside</td>
<td></td>
</tr>
</tbody>
</table>

16-17 October 2008 OECD Knowledge Markets 28
Clinical trial summary from the National Cancer Institute's PDQ® database

Publications indexed to this study:


Study ID Numbers: CDR0000069374, MRC-LY10, EU-26117
First Received: July 8, 2002
Last Updated: August 23, 2008
ClinicalTrials.gov Identifier: NCT00040590
Health Authority: United States: Federal Government

Keywords provided by National Cancer Institute (NCI):
untreated adult acute lymphoblastic leukemia
L3 adult acute lymphoblastic leukemia
stage I adult Burkitt lymphoma
stage III adult Burkitt lymphoma
stage IV adult Burkitt lymphoma
contiguous stage II adult Burkitt lymphoma
noncontiguous stage II adult Burkitt lymphoma

Study placed in the following topic categories:
Leukemia, Lymphoid
Lymphoma, small cleaved-cell, diffuse
Leucovorin
Cyclophosphamide
Etoposide phosphate
Acute lymphoblastic leukemia, adult
Lymphoma, B-Cell
Leukemia
Burkitt's lymphoma
Methotrexate

Immunoproliferative Disorders
Vincristine
Doxorubicin
Herpesviridae Infections
Folic Acid
Virus Diseases
Lymphatic Diseases
Ifosfamide
Burkitt Lymphoma
B-cell lymphomas
To PubMed Journal Citation

A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCTI LY10 trial).


This prospective study aimed to develop reproducible diagnostic criteria for sporadic Burkitt lymphoma (BL), applicable to routine practice, and to evaluate the efficacy of dose-modified (dm) CODOX-M/IVAC in patients diagnosed using these criteria. The study was open to patients with an aggressive B-cell lymphoma with an MKI67 fraction approaching 100%. Immunophenotype and fluorescent in situ hybridization (FISH) were used to separate BL from other aggressive B-cell lymphomas. BL was characterized by the presence of a dMYC rearrangement as a sole cytogenetic abnormality occurring in patients with a germinal center phenotype with absence of BCL-2 expression and abnormal TP53 expression. A total of 128 patients were eligible for the study, of whom 58 were considered to have BL and 70 to have diffuse large B-cell lymphoma (DLBCL). There were 110 clinically fit patients who received dmCODOX-M (methotrexate, dose 3

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Clinical Trials and Observations

A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial)

Graham M. Mead,1 Sharon L. Barrans,2 Wendi Qian,3,4 Jan Walewski,4 John A. Radford,5 Max Wolf,6 Simon M. Clawson,3 Sally P. Stenning,3 Claire L. Yule,3 and Andrew S. Jack2, on behalf of the UK National Cancer Research Institute Lymphoma Clinical Studies Group and the Australasian Leukaemia and Lymphoma Group

1Southampton University Hospitals Trust, Southampton, United Kingdom;

2Haematological Malignancy Diagnostic Service, Leeds General Infirmary, Leeds, United Kingdom;

3MRC Clinical Trials Unit, London, United Kingdom;

4MSCM Cancer Center, Warsaw, Poland;

5Christie Hospital, Manchester, United Kingdom, and

6Peter MacCallum Cancer Centre, Melbourne, Australia
Coming full circle: Link back to ClinicalTrials.gov

Abstract

This prospective study aimed to develop reproducible diagnostic criteria for sporadic Burkitt lymphoma (BL), applicable to routine practice, and to evaluate the efficacy of dose-modified (dm) CODOX-M/IVAC in patients diagnosed using these criteria. The study was open to patients with an aggressive B-cell lymphoma with an MKI67 fraction approaching 100%. Immunophenotype and fluorescent in situ hybridization (FISH) were used to separate BL from other aggressive B-cell lymphomas. BL was characterized by the presence of a cMYC rearrangement as a sole cytogenetic abnormality occurring in patients with a germinal center phenotype with absence of BCL-2 expression and abnormal TP53 expression. A total of 128 patients were eligible for the study, of whom 58 were considered to have BL and 70 to have diffuse large B-cell lymphoma (DLBCL). There were 110 clinically fit patients who received dmCODOX-M (methotrexate, dose 3 g/m²) with or without IVAC according to risk group. The 2-year progression-free survival was 64% (95% confidence interval [CI] 51%-77%) for BL, 55% (95% CI 42%-66%) for DLBCL, 85% (95% CI 73%-97%) for low risk, and 49% (95% CI 38%-60%) for high-risk patients. The observed differences in outcome and other clinical features validate the proposed diagnostic criteria. Compared with the previous trial LY06 with full-dose methotrexate (6.7 g/m²), there was a reduction in toxicity with comparable outcomes. This study was registered at www.clinicaltrials.gov as NCT00040690.
Future integration with other NLM Resources

1. PubMed
   - Search PubMed for anti-influenza treatment prevention
   - Comparison of the anti-influenza virus activity of RWJ-270201 with those of oseltamivir and zanamivir.

2. Chemical Structures in Article
   - FIG. 1. Structures of compounds under investigation
     - Zanamivir
     - Oseltamivir
     - RWJ-270201 bound to neuraminidase

3. PubChem
   - Compound Summary: RWJ-270201

4. 3-D View of Chemical and Protein
   - RWJ-270201 bound to neuraminidase
Complementary NIH Policies for Data Sharing and Access

• NIH Data Sharing Policy
  – Applies to funded researchers who receive >USD 500,000 from NIH in a single year
  – Expected to include with their grant proposal a plan for making research data available to other researchers.

• NIH Public Access Policy
  – Applies to all funded investigators and NIH researchers
  – Required to submit peer reviewed manuscripts to PubMed Central upon acceptance for publication
  – Up to 12 delay before manuscript is publicly available

• NIH Genome Wide Association Study (GWAS) Policy
  – Applies to funded investigators for GWAS
  – Submit de-identified genotypic and phenotypic data to NLM Database of Genotype and Phenotype (dbGaP).
  – Other investigators may request access to GWAS data sets for research purposes.
Additional information

ClinicalTrials.gov:
http://www.clinicaltrials.gov

NIH Public Access Policy:
http://publicaccess.nih.gov/

PubMed Central:
www.pubmedcentral.nih.gov

National Library of Medicine
www.nlm.nih.gov

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