Creation of a Chronic Myeloid Leukemia Retrospective Outcomes Research Registry

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Research Funding

• Brixner (PI) 08/11/2010 - 12/31/2012
• Novartis Pharmaceuticals Corp.
• **Resource Utilization for the Management of Chronic Myeloid Leukemia in a Comprehensive Cancer Center Network Database**
• Goals: Profile CML patients by treatment and severity at diagnosis and
  – Track subjects’ progression through chronic, accelerated and blast phases of CML
  – Develop and utilize an algorithm to identify CML phases in our population
  – Evaluate resource use pre and post treatment (when given) within each phase,
  – Evaluate efficacy, safety outcomes, and length of survival post diagnosis according to CML phase and treatment.
Personnel

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• Brian Oberg – PORC
• Blaine Osborne – PORC
• Scott Silverstein - HCl
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• Amy Guo – Novartis
• Vamsi Bollu – Novartis
• Regan Healy – Intermountain Health
Research Oversight and Approval

• Access to protected health information (PHI) of Huntsman Cancer Institute based upon required appropriate approvals

  – Institutional Review Board (IRB)
  – Clinical Cancer Investigations Committee (CCIC)
  – Conflict of Interest (COI) – for all researchers
  – Resource for Genetic and Epidemiological Research (RGE)
About this Project

• **Describes**
  – *use* of different resources in the treatment of chronic myeloid leukemia

• **stratifies resource use by**
  – treatment and relevant clinical outcomes,
  – including morbidity and mortality (length of survival).

• **Raison d'être:** As health authorities around the world make decisions on reimbursement for new expensive treatments in cancer,
  – there is an increasing demand for real world EMR evidence on the outcomes and costs of these treatments. Using a retrospective study complements other methods (clinical trials, claims database research).
  – In CML, the response rates and survival can be difficult to capture in a claims database, or in a national ambulatory care electronic medical record system, to link to costs for reimbursement decisions. A retrospective study design can addresses these shortcomings.
  – The goal of our study was to evaluate CML patients receiving TKI treatment to assess their demographics (including Charlson Comorbidity Scores) and outcomes through treatment response and survival.
  – These data can be further explored to provide real world evidence in decision making.
Chronic Myeloid Leukemia (CML)

• 15% of all leukemias
• 4,000-5,000 new cases annually
• Male to female 2:1
• Median age at diagnosis 65 yrs
• Median age at death 74 yrs
Incidence and Mortality

Pathogenesis

• Philadelphia chromosome discovered in 1960
• Reciprocal translocation t(9;22)
  — Resulting in the formation of the BCR-ABL chimeric gene
  — Constitutively active tyrosine kinase
Clinical Manifestations

• Many diagnosed as a result of an abnormal complete blood count

• Common presenting symptoms related to:
  — Anemia
  — Splenomegaly (most common physical finding)
  — Increased cell turnover—leukostasis
Phase Definitions

**Chronic Phase:** <10% blasts
- Duration
  - 3-5 years pre Tyrosine Kinase Inhibitor (TKI)
  - 13-15 years post TKI

**Accelerated Phase:** ≥10-19% blasts
- Duration 6-12 months
  - Highly symptomatic
  - Financial burden
  - High resource utilization
  - High mortality

**Blast Crisis:** ≥ 20-30% blasts
- Duration 6-12 months
- Rapid progression

Laboratory Testing

**Cellular level**
- **Hematologic**
  - Peripheral blood
    - WBC: >25 x10^9/L
    - Blasts 0-15%
  - Bone Marrow
    - Hypercellular
    - Blast count

**Chromosome level**
- **Cytogenetic**
  - Analysis of 20 metaphases for detection of t(9;22)
  - FISH

**DNA level**
- **Molecular**
  - RT-PCR
  - Presence of BCR-ABL fusion gene
Treatment Response

- Diagnosis or Hematologic Relapse
- Complete Hematologic Response
- Complete Cytogenetic Response
- Major Molecular Response
- Undetectable transcript (Complete Molecular Response)

Development of Treatments

- Palliative therapy
  - Arsenic
  - Spleen irradiation
  - Busulfan
  - Hydroxyurea
- Curative therapy
  - Stem cell transplantation
  - Combination chemotherapy
  - Interferon alpha
  - Imatinib
  - Dasatinib, nilotinib

Initial Treatment

Tyrosine Kinase Inhibitors (TKI)

- Imatinib 400 mg PO daily
  - FDA approval May 2001

- Dasatinib 100 mg PO daily
  - FDA approval June 2006 and 2010 for first line treatment

- Nilotinib 300 mg PO BID
  - FDA approval October 2007 and 2010 for first line treatment
Primary Study Objectives

• Develop and utilize an algorithm to identify CML patients by phases in our population based on ICD-9 identification followed by chart review confirmation of CML diagnosis.
  – The work from this objective established a solid foundation for the accuracy of using ICD-9 coding vs. further restrictions and validation to accurately identify a group of CML patients.

• Evaluate resource utilization pre- and post treatment (when given) within each phase.
  – Treatment choices were determined at baseline and throughout care for patients from diagnosis, to either death or end of follow up or December 31, 2010, which ever came first.

• Evaluate efficacy, safety (ADE), outcomes (time to progression and survival), and length of survival post.
  – Our study confirmed survival benefit for TKI therapy and also monitored time to progression, remission, relapse through evaluation of response by cytogenetic, hematological and molecular response.
Data Sources
Study Population and Final Cohort

• Our study utilized a combination of the University of Utah Enterprise Data warehouse and the Utah Population Database to develop a cohort of 606 CML patients identified by ICD-9 codes.

• The electronic notes of the 606 patients were manually reviewed to identify patients receiving treatment at HCI.
  – This population was validated against the Huntsman Cancer Institute CML tumor registry to confirm diagnosis, leaving us with a population of 234 patients 1995 to 2010.
Cohort Selection

• **Inclusion Criteria**
  – Age $\geq$18 years on index date
  – ICD-9 code 205.1X.
  – Ph1 positive or BCR-ABL positive lab results
  – Diagnosis confirmed by chart review

• **Exclusion Criteria**
  – Inadequate history prior and post the index date
  – Patients with a Philadelphia negative chromosome test result
  – Patients without validation of CML diagnosis by physician notes and lab results.
ICD-9 and ICD-O Coding to Identify Patients

**ICD-9CM Codes – EDW Identification**

<table>
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<tr>
<th>ICD-9 Dx Code</th>
<th>Description / Meaning</th>
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<tr>
<td>205.1</td>
<td>Chronic myeloid leukemia</td>
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<tr>
<td>205.10</td>
<td>CML, without mention of having achieved remission</td>
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<td>205.11</td>
<td>CML, in remission</td>
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<tr>
<td>205.12</td>
<td>CML, in relapse</td>
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**ICD-O Codes – HCI Tumor Registry Identification:**

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<tr>
<th>Site.subsite Code</th>
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<th>Behavior Code</th>
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<td>C42.1 M-9876/3</td>
<td>Atypical chronic myeloid leukemia, BCR/ABL negative</td>
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</table>
Methodology –
Cohort Selection (Patient Flow Diagram)
EDW patient population 1995-2010 N=1,240,47

Patients age ≥ 18 N= 965,460

Patients with min one CML Dx by ICD-9 & one encounter N= 606

Patients with CML Dx confirmed by chart review N= 234

Males
N= 140

Females
N= 94

Number of new cases by year

1995 N= 7
1996 N= 16
1997 N= 21
1998 N= 18
1999 N= 19
2000 N= 13
2001 N= 20
2002 N= 14
2003 N= 8
2004 N= 16
2005 N= 11
2006 N= 13
2007 N= 17
2008 N= 16
2009 N= 15
2010 N= 9

Patient Flow Diagram
Methodology –
Cohort Section, Detail

- At least 1 ICD-9 code for CML
  - n = 606

  - Lab result indicative of CML
    - n = 174

  - Chart review indicative of CML
    - n = 60

  - CML confirmed cohort
    - n = 234

- Tumor registry CML positive
  - n = 177

  - At least 2 ICD-9 codes for CML
    - n = 385
Methodology – Overall Study Design

• Retrospective database study
• Cross-sectional analysis of patients with CML from 1995 to 2010
  – evaluate CML patients within an integrated cancer network database to assess resource use, clinical outcomes, tolerances as toxicities categorized by treatment and severity.
    • Develop and utilize an algorithm to identify CML phases in our population based on ICD-9 identification followed by chart review confirmation of CML diagnosis.
    • Evaluate resource utilization pre- and post treatment (when given) within each phase.
    • Evaluate efficacy, safety (ADE), outcomes (time to progression and survival), and length of survival post diagnosis according to CML phase and treatment
Methodology – Data Sources

• UUHSC Enterprise Data Warehouse (EDW)
• Utah Population Database (UPDB)
Methodology – EDW

- **EDW integrates the comprehensive electronic medical record** (EMR) for patients, including all cancer cases across the University of Utah Healthcare Sciences (UUHS), the Huntsman Cancer Institute and the Hospital (HCI/HCH).
- The EDW provided the clinical data that included electronic notes, lab orders and results, medication orders, and in certain cases death certificates data.
  - If the patient died in UUHS-HCI/HCH then the EDW will contain the death certificate data, including date of death and cause(s) of death (as an ICD-9 code).
  - The health care text data in the EMR of a subject originates from the physician created notes section in a subject’s EMR.
Methodology - UPDB

• In those cases where the death occurred external to UUHSC services it was necessary to look to the UPDB for extant death certificates of patients in the cohort.
  – match subjects between EDW and UPDB by the master patient index (MPI).
  – The UPDB is as much as 1 year behind in linking to death certificates of the State of Utah.
• The UPDB has been linked to the Utah Cancer Registry records from 1966 ~ 2011; ~ 6 month lag.
  – Death certificates dating back to 1904.
  – Originally was derived by computerization of Church of Latter Day Saints Group Sheets (~ 1.6 million individuals) → genealogy – wide and deep to understand genetic predisposition to cancer by Mark Skolnick and colleagues.
  • Initiated in the late seventies via a federal grant by Mark Skolnick who came to Utah to create a resource to demonstrate that cancer had a genetic basis.
  – Grows annually through updates from the Utah Department of Health for births, deaths, marriages, and divorces, as well as records from the Utah Driver’s License Division, in addition to new information from the UCR.
  – The UPDB has more than 14.9 million records and has 6.5 million unique individuals based upon person oriented record linking analysis.
  – Under jurisdiction for the UU-HCI Resource for Genetic and Epidemiological Research (RGE).
Methodology – Text Search and Chart Review

• This study used *physician notes* stored electronically (MDe-notes) in the electronic medical record (EMR is the EDW) for each subject.

  – Two step process where data was quantified in the **phase I** and analyzed in the **phase II** process.
Methodology – Phase I of MDe-notes Analysis

- Phase-I focused on determining the number of instances, counts, or “hits” for a particular keyword or key-phrase in the electronic narrative for each CML patient of the cohort. The automated text search scan was performed assessing all notes available in the patients’ electronic chart in EDW including physician notes, nurse notes and lab results. The steps for the text search were as follows:

- A clinical expert looked through the lab results available to confirm the diagnosis of CML. In addition, the automated text search tool was used to search for text indications of CML. After evaluating the results of the searches for each patient (chart review), a clinical expert was able to identify whether the patient had a diagnosis of CML. The defined diagnosis of CML was done after the confirmation of the condition in at least 2 keyword search results.

- After the CML confirmed cohort was redefined, a clinical expert defined all the relevant questions to be answered about the specific cohort studied to provide data needed for analysis plan and generated relevant terms for each search.

- An automated text search program scanned all the notes for the specific cohort, searching for the relevant terms provided by the clinical expert.

- Each query contained all note files that included the searched term +/- 100 characters around the search term. The first time a specific term was found in a record it was highlighted to help clinical experts to identify different patients. The search term was also boldfaced in all entries.

- Phase II included the analysis of the new codified data by medication treatment, phase and disease progression.
Methodology –
Phase II of MDe-notes Analysis
(Manual Review and Adjudication of Text String Hits from Phase-I)

• **Objective** - manually identify stage, drug use, stage and response to treatment
  – adjudicate, or validate the results of Phase-I meaning of the clinical narrative by automated text searching.
  – Reviewer evaluation (by pharmacists) of text search notes, previously gathered from phase 1 and validation of the results. Followed by an oriented chart review
  – Standardization of data, based on the interpretation of the notes included in the electronic medical charts was entered into the analysis the database to help identify sub-cohorts in future steps.
  – Stage and drug use cohort were defined to help the interpretation of data.
  • Time cohorts of ≤18 months, 19-36 months and >36 months post index data were created. The next step included a set of clinical questions that needed to be answered in order to complete the Tables from the analysis plan.
Methodology – Subject Classification

• Included patients based on the following criteria describing the different phases of CML.

• Defined stage at diagnosis based on the electronic physician’s notes in the EHR.
  – based upon World Health Organization (WHO) criteria.
  – For the course of disease, the stages to determine progression or remission and response with be identify in the charts, when available and validated by a hematological-pathologist at HCI/HCH, based on lab results.
Methodology – Charlson Comorbidity Index (CCI)

• The Charlson Comorbidity Index (CCI) encompasses 17 medical conditions (ICD-9) weighted 1–6.

• From the weighted conditions, a sum score can be tallied to yield the total comorbidity score.

• To account for increasing age, one point is added to the CCI score for each decade of life over the age of 50 (1 point for 51-60, 2 points for 61-70, 3 for 71-80 and 4 for >80.).

• Thus, possible CCI scores range from 0 to 34.
# Charlson Comorbidity Scoring Table

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>D’Hoore ICD-9 Codes</th>
<th>Charlson Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>410, 411</td>
<td>1</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>398, 402, 428</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>440-447</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>430-433, 435</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>290, 291, 294</td>
<td>1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>491-493</td>
<td>1</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>710, 714, 725</td>
<td>1</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>531-534</td>
<td>1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>571, 573</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>250</td>
<td>2</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>342, 434, 436, 437</td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe renal disease</td>
<td>403, 404, 580-586</td>
<td>2</td>
</tr>
<tr>
<td>Any tumor</td>
<td>140-195</td>
<td>2</td>
</tr>
<tr>
<td>Leukemia</td>
<td>204-208 (not 205.1)</td>
<td>2</td>
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<tr>
<td>Lymphoma</td>
<td>200, 202, 2003</td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>070, 570, 572</td>
<td>3</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>196-199</td>
<td>6</td>
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</table>

Methodology – Subject Classification

• Included patients based on the following criteria describing the different phases of CML.
  – Stage at diagnosis based on the physician’s notes
  – In accordance to the world health organization (WHO) criteria.
    • For the course of disease, the stages to determine progression or remission and response were identified in the charts, when available and validated by a hematological-pathologist at HCI/HCH, based on lab results.
Methodology – Study outcomes

• Treatment response rates,
• Overall survival
• Medication tolerability
• Each of the above were evaluated on index date forward.
  – Variables for outcomes or stage were fleshed out by categories:
    • drugs, CPT codes, diagnosis, laboratory tests, histological data, other attributes and validated with EDW staff (IT) and UUHS-HCI/HCH staff (clinical, i.e., pharmacist and physician).
NCCN Outcomes
Methodology – “Time to event” Outcomes

- The following outcomes at different phases after initiation of treatment were of interest:
  - Response rate, time to response, time to disease relapse
  - Time to disease progression from chronic phase, and trends in CML of genetic mutation and potential resources
  - Events related to death:
    - Overall survival
    - Overall, cause of death
    - Cause of death by initial drug therapy
    - Time to death by initial treatment
    - time to disease progression
  - Treatment failures at time ≤18 months, 19-36 months and > 36 months were also evaluated
Methodology – Medication Treatment Outcomes

- Medication tolerability
- Medication switch, discontinue
- Frequency of toxicities/adverse events for treatments
- Time to toxicities/adverse events for treatments
Methodology – Additional Independent Variables

• Other independent variables were identified to describe the patient cohort, and to control for characteristics that may influence outcomes or otherwise bias findings.
  – Treatment of choice was identified on index date
  – The subjects were followed forward. Demographic and clinical characteristics were as recorded on index date
  – Priority for capturing baseline values were given to the observation on index date or the closest value reported up to one year after the index date
  – If no values are reported post index date, the value reported closest to and up to one year pre-index date was captured
  – This approach minimized confounding due to drug therapy being initiated during the observation window but after the outcome value was captured
Methodology – Statistical Analyses

• **Descriptive statistics**, including mean, standard deviation, frequency and percentage for continuous and categorical variables respectively, were utilized to describe demographic characteristics (age, sex, region of residence, plan type and race), baseline clinical characteristics (i.e., WBC, blasts, basophils, LDH, spleen size, platelet, thyroid, neutrophil, and ECG) and comorbidities.

• Patients identified with CML from the EDW were categorized by chronic, accelerated, and blast phases.

• For continuous variables, ANOVA was used to identify differences in chronic phase, accelerated phase, and blast phase of CML. For categorical variables, $\chi^2$ test was used for testing the differences between the cohorts. To test the significance of the survival data, log rank was the statistical test used.

• Demographic data, drug treatments, and co-morbid conditions for CML patients were collected at the time of first CML diagnosis (index date). Multivariate linear or logistic regression models were developed to examine the association between baseline characteristics and clinical outcomes (treatment and toxicities) for the CML cohort.

• For time to event, the median time to event was reported when every single patient had the response to the outcomes. Otherwise, a Kaplan-Meier curve will be developed to compare the survival function between the cohorts for each individual treatment.

• All statistical tests were performed at an a priori significance level of 0.05 using Stata SE v. 10 (StataCorp, College Station, TX). The protocol for this study was presented to the University of Utah Institutional Review Board for approval prior to commencing data analysis.
Methodology –
Criteria for Cytogenetic, Hematologic, and Molecular Response

• **Complete hematologic response**
  – Complete normalization of peripheral blood counts with leukocyte count < 10 x 10^9/ L
  – Platelet count < 450 x 10^9/ L
  – No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood
  – No signs and symptoms of disease with disappearance of palpable splenomegaly

• **Partial hematologic response**
  – Presence of immature cells
  – Platelet count < 50% of the pretreatment count, but > 450 x 109/L
  – Persistent splenomegaly, but < 50% of the pretreatment extent

• **Cytogenetic response**
  – Complete- No Ph1-positive metaphases
  – Partial-1%-35% Ph1-positive metaphases
  – Major- 0%-35% Ph1-positive metaphases
  – Minor- >35% Ph1-positive metaphases

• **Molecular response**
  – Complete molecular response- BCR-ABL mRNA undetectable by RT-PCR
  – Major molecular response- ≥3-log reduction of BCR-ABL mRNA or <0.1 on IS scale

If you need access to the Cohort Targeted Chart Review application, or are having problems logging in, please submit a trouble ticket or contact the UIT Hospital Help Desk at 587-6000.

Site Contact: corpradar@hsc.utah.edu
Cohort Selection

**CHOOSE AN AVAILABLE COHORT**

- BCCONF
- BREAST
- CML
- CMLCONF
- CNS
- HCC1AND2
- HCC3A
- HCC3BAND4
- HCCCONF
- HCCINOPER
- HCCMETAST
- HCCNONCCN
- HCCNOSTGE
- HCCPOTENT
- HCCTRANSP
- HCCUNRESE
- MELANOMA
- NSCLC
- NSCLC_TR
- OVARY
### Menu Selection

#### Cohort Targeted Chart Review

<table>
<thead>
<tr>
<th>COHORT LIST</th>
<th>SIMPLE TEXT SEARCH</th>
<th>BOOLEAN TEXT SEARCH</th>
<th>ADD QUESTION</th>
<th>CHART REVIEW</th>
</tr>
</thead>
</table>

#### BOOLEAN TEXT SEARCH

- **COHORT**
- **SUBCOHORT (RESTRICT TO MRN FROM A PREVIOUS SEARCH)**
- **SEARCH TERM**
- **SEARCH NAME**
- **TIME FRAME START (DAYS FROM DIAGNOSIS)**
- **TIME FRAME END (DAYS FROM DIAGNOSIS)**

#### Table

<table>
<thead>
<tr>
<th>COHORT</th>
<th>SUBCOHORT</th>
<th>SEARCH NAME</th>
<th>TERMS SEARCHED</th>
<th>TIME FRAME</th>
<th>TOTAL RECORDS FOUND</th>
<th>TOTAL PATIENTS WITH RECORDS</th>
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**Submit**
## Search Terms

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<th>COHORT</th>
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<td>CML general medication search</td>
<td>MEDICATIONS</td>
<td>16304</td>
<td>559</td>
</tr>
<tr>
<td>CML</td>
<td>CMML</td>
<td>CMML</td>
<td>1336</td>
<td>59</td>
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</tbody>
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# Search Output

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>RPT TYPE</th>
<th>TEXT DATE</th>
<th>SUBTEXT WHERE TERM FOUND</th>
<th>RPT ID</th>
</tr>
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<tbody>
<tr>
<td>MTS</td>
<td>OPR</td>
<td>{ts '1998-10-28 00:00:00'}</td>
<td>She was admitted to the ICU because she has multiple medical problems including CML, atrial fibrillation, bad lungs, and she had renal failure. She was also developing fevers and</td>
<td>2447996</td>
</tr>
<tr>
<td>MTS</td>
<td>OPR</td>
<td>{ts '2006-08-23 00:00:00'}</td>
<td>ne. DISPOSITION: To MICU in stable condition. BRIEF HISTORY: Patient is a 58-year-old male with CML who was subsequently transformed to AML. He was admitted for chemotherapy. He had been complaining</td>
<td>10189623</td>
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<td>CERNER</td>
<td>OPR</td>
<td>{ts '2006-08-23 00:00:00'}</td>
<td>ne. DISPOSITION: To MICU in stable condition. BRIEF HISTORY: Patient is a 58-year-old male with CML who was subsequently transformed to AML. He was admitted for chemotherapy. He had been complaining</td>
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<tr>
<td>CERNER</td>
<td>PTT</td>
<td>{ts '2006-08-24 00:00:00'}</td>
<td>openness CURRENT PROBLEM: assess mobility and safety PAST MEDICAL HISTORY: crani (as child), CML-like MDS, bone marrow biopsy (12/05), arthritis Information received: per chart. PRECAUTIONS</td>
<td>10191063</td>
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<tr>
<td>CERNER</td>
<td>PTT</td>
<td>{ts '2006-09-26 00:00:00'}</td>
<td>ion was performed. Patient is a 58-year-old C M, admitted on 08/09/2006 15:21:00. DIAGNOSIS: CML, right posterior hip pain secondary to BM biopsy. CURRENT PROBLEM: right posterior hip pain</td>
<td>10364053</td>
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</table>
Question entry and answer

Add new question to CML cohort:

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>ANSWER TYPE</th>
<th>DROP DOWN OPTIONS (PLEASE SEPARATE OPTIONS BY &quot;/&quot;)</th>
<th>PARENT QUESTION</th>
<th>CHILD QUESTION ORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent on interferon?</td>
<td>YES/NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient on hydroxyurea</td>
<td>YES/NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient on cytarabine (ara-C)?</td>
<td>YES/NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient on Nilotinib (Tasigna)</td>
<td>YES/NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient on Dasatinib (Sprycel)</td>
<td>YES/NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient on IMATINIB</td>
<td>YES/NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PATIENT HAS CML?</td>
<td>YES/NO</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Existing questions for CML
# Data view

<table>
<thead>
<tr>
<th>PATID ALIAS</th>
<th>DIAG DATE</th>
<th>DIAG AGE</th>
<th>DIAG DATE SRC</th>
<th>DIAG YEAR</th>
<th>DEATH YEAR</th>
<th>GENDER</th>
<th>CCI SUM</th>
<th>CML CONFIRMED</th>
<th>DAVID LABREVIEWS</th>
<th>COD10 UPDB</th>
<th>COD1 UPDB</th>
<th>COD2 UPDB</th>
<th>COD3 UPDB</th>
<th>COD4 UPDB</th>
<th>COD5 UPDB</th>
<th>COD6 UPDB</th>
<th>COD7 UPDB</th>
<th>COD8 UPDB</th>
<th>COD9 UPDB</th>
<th>DDATE UPDB</th>
<th>DIAGTYPE UPDB</th>
<th>ICD9 DIAG COUNT</th>
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<tbody>
<tr>
<td>1669</td>
<td>08/06/2008</td>
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<td>R688</td>
<td>C920</td>
<td>C921</td>
<td></td>
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<td>1672</td>
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<td>11/10/2007</td>
<td>ICD10</td>
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</tbody>
</table>
Data view: chart review questions

<table>
<thead>
<tr>
<th>Stage of diagnosis</th>
<th>Bone Marrow Transplant</th>
<th>Hyper-CVAD Induction?</th>
<th>Patient Has CML?</th>
<th>Patient On Busulfan?</th>
<th>Patient On Imatinib</th>
<th>Patient On Dasatinib (Sprycel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>no</td>
<td></td>
<td>YES</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic</td>
<td>yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>yes</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>NO</td>
<td></td>
<td>YES</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

• Overall results
• Subgroup analysis for an ASCO abstract
Demographics

• Confirmed CML cases = 234
  – 59.8% Male
  – Mean age 46 years
  – 61% Caucasian, 28% unknown
  – 66% from Utah
Insurance Type

<table>
<thead>
<tr>
<th>Type</th>
<th>Number of Patients</th>
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</thead>
<tbody>
<tr>
<td>Commercial</td>
<td>123</td>
</tr>
<tr>
<td>Medicare</td>
<td>49</td>
</tr>
<tr>
<td>Medicaid</td>
<td>15</td>
</tr>
<tr>
<td>Self pay and unfunded</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
</tr>
<tr>
<td>Unknown</td>
<td>24</td>
</tr>
</tbody>
</table>
Stage at Diagnosis

- Accelerated Phase: 5%, n = 12
- Blast Phase: 2%, n = 5
- Chronic Phase: 93%, n = 211
Charlson Comorbidity Score

Number of Patients

0: 65
1: 38
2: 64
≥3: 67

Comorbidity Score
Initial Treatment (n = 234)

- Nilotinib: 1
- Chemotherapy regimen: 2
- Other: 4
- Interferon-α + Hydroxyurea: 4
- Interferon-α + Cytarabine: 4
- Unknown: 6
- Dasatinib: 6
- Busulfan: 8
- Hydroxyurea: 17
- Interferon-α: 30
- Bone Marrow Transplant: 39
- Imatinib: 113
### Drug therapy Pre TKI era (<2001)

$n = 94$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib</td>
<td>0</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>0</td>
</tr>
<tr>
<td>Interferon-α + Cytarabine</td>
<td>1.1</td>
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<tr>
<td>Chemotherapy regimen</td>
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</tr>
<tr>
<td>Unknown</td>
<td>2.1</td>
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<tr>
<td>Interferon-α + Hydroxyurea</td>
<td>4.3</td>
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<tr>
<td>Imatinib</td>
<td>5.3</td>
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<tr>
<td>Busulfan</td>
<td>6.4</td>
</tr>
<tr>
<td>Other</td>
<td>11.7</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>28.7</td>
</tr>
<tr>
<td>Bone Marrow Transplant</td>
<td>38.3</td>
</tr>
</tbody>
</table>
Drug therapy Post TKI era (>2001)
n = 140

- Nilotinib
- Chemotherapy regimen
- Other
- Busulfan
- Interferon-α + Cytarabine
- Interferon-α
- Bone Marrow Transplant
- Unknown
- Dasatinib
- Interferon-α + Hydroxyurea
- Imatinib

Percentage of Patients

0 10 20 30 40 50 60 70 80 90 100 77.2
Drug therapy Pre and Post TKI era

- Nilotinib
- Chemotherapy regimen
- Other
- Busulfan
- Interferon-α + Cytarabine
- Interferon-α
- Bone Marrow Transplant
- Unknown
- Dasatinib
- Interferon-α + Hydroxyurea
- Imatinib

Percentage of Patients

- >2001
- <2001
TKI Utilization at Anytime

![Bar Chart]

- **Imatinib**: 143
- **Dasatinib**: 27
- **Nilotinib**: 8

**Y-axis**: Number of Patients

**X-axis**: TKI Types (Imatinib, Dasatinib, Nilotinib)
ASCO Abstract

- Diagnosed in Chronic Phase 2001-2010
- Imatinib first line treatment
- Assessed utilization and outcome of cytogenetic and molecular testing with 18 months of therapy initiation
  - Complete Cytogenetic Response = No Ph+ Cells by chromosome analysis or FISH
  - Major Molecular Response = <0.1 BCR/ABL transcripts
  - ADE rate
Cytogenetic or molecular testing within 18 months: n = 50, 54.3%

No testing within 18 months:
- No testing at anytime: n = 26, 28.3%
- No testing within 18 month, but testing >18 months: n = 16, 17.4%

Testing at anytime: n = 66, 71.7%

Distribution of patients with and without cytogenetic or molecular testing
Reasons for lack of disease monitoring within 18 months

<table>
<thead>
<tr>
<th>Reason</th>
<th>No Disease monitoring within 18 mo</th>
<th>No disease monitoring &lt;18 mo, but had disease monitoring &gt;18 mo (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician Choice not to monitor</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Monitored at OSH</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Diagnosed at outside hospital and presented to HCl &gt;18 mo after initiating therapy</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Not treated at HCl</td>
<td>22</td>
<td>3</td>
</tr>
</tbody>
</table>
Reasons for lack of disease monitoring within 18 months

- No disease monitoring <18 mo, but had disease monitoring >18 mo (n = 16)
  - Not treated at HCl: 3
  - Diagnosed at outside hospital and presented to HCl >18 mo after initiating therapy: 10
  - Monitored at OSH: 3
  - Physician Choice not to monitor: 0

- No Disease monitoring within 18 mo (n = 42)
  - Not treated at HCl: 22
  - Diagnosed at outside hospital and presented to HCl >18 mo after initiating therapy: 13
  - Monitored at OSH: 6
  - Physician Choice not to monitor: 1
ASCO: Reasons for No Disease Monitoring within 18 months (n = 42)

- Physician Choice not to monitor
  - Disease Monitoring >18 mo (n = 16)
  - No Disease Monitoring within 18 mo (n = 42)

- Monitored at Outside Hospital
  - 7%

- Diagnosed at outside hospital and presented to HCl >18 mo after initiating therapy
  - 24%

- Not treated at HCl for CML
  - 52%
ASCO: Disease Monitoring Utilization and Outcome (n = 92)

Median Time to CCyR = 241 days
Median Time to MMR = 254 days
Unique patients with either test = 50

- **Cytogenetic**: 49% (36% of monitored)
  - Testing completed: 73%
  - Response (CCyR or MMR): 26%

- **Molecular**: 52%
  - Testing completed: 50%
  - Response (CCyR or MMR): 26%
Patients Achieving a CCyR or MMR within 18 months

Median Time to CCyR = 241 days
Median Time to MMR = 254 days
Patients Achieving a CCyR or MMR at anytime

Median Time to CCyR = 241 days
Median Time to MMR = 254 days
ASCO: Imatinib Associated Adverse Events

- ADE of any grade (n =60)
  - 42 patients (46%)
- ADE resulting in dose reduction
  - 15 patients (36%)
  - Median of 77 days
- ADE resulting in discontinuation of imatinib
  - 9 patients (21%)
  - Median of 130 days
ASCO: Suboptimal response or failure

- Imatinib dose increased to >400 mg
  - 21 patients (23%)
  - Median of 457 days

- Change in therapy to Dasatinib or Nilotinib
  - 8 patients—25% of patients diagnosed from 2006-2010
    - Reasons for change:
      - Suboptimal response or treatment failure = 5 patients
      - ADE to imatinib = 3 patients
UPDB: Cause of Death
Assumed Alive = 163; Dead = 71
Survival Estimates by Stage

Kaplan-Meier survival estimates

ACCELERATED

BLAST

CHRONIC

analysis time

Graphs by Stage_Dx
Survival Estimates by Initial Treatment

Kaplan-Meier survival estimates

- bone marrow transplant
- busulfan
- chemotherapy regimen
- clinical trial
- cytarabine SQ + daunorubicin
- cytarabine SQ + interferon-alfa
- dasatinib
- hydroxyurea
- imatinib
- interferon-alpha
- interferon-alpha + hydroxyurea
- nilotinib
- splenectomy
- unknown

analysis time
Conclusions

• Individual data sources containing non-integrated data components can be used to assess:
  – Outcomes
  – Resource use
  – Charges
Conclusions

• CML patients at the Huntsman Cancer Institute:
  – Younger than national data (45 yrs vs 65 yrs)
  – Have comorbidities reflective of their age
  – Imatinib CCyR and MMR rates similar to registration trials
  – ADEs reflective of TKI side effect incidence and type
  – Survival indicative of TKI-era
  – High utilization rate of TKIs (61%)
  • High transplant rate pre-TKI era
Advantages of EDW data

• Rich data source
  – Demographic
  – Disease
    • Comprehensive
    • Unfiltered
  – Medication
  – Procedure
  – Laboratory
  – Charge
• Linked to other data sources—UPDB (survival)
• No upfront costs for data source
Challenges with EDW data

• Disparate data sources—data not federated
• No common ontology
• Lack of coding standards
• Change in data input over time (change in vendors)
• No data dictionary!
• Complexity of data management
• Expensive in personnel time
Future Directions

• Internal collaboration
  – Quality of life analysis
  – Adherence to NCCN guidelines

• External collaboration
  – Austrian colleagues
  – IHC
  – Other NCCN centers