Treatment of Adolescents and Young Adults with ALL with an Asparaginase-Intensive Pediatric Regimen

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DFCI ALL Consortium

- Randomized, multi-institutional clinical trials since 1973
- Historically, enrolling patients 0-18 years of age
  - Recently expanded to include adults with ALL (up to age 50 years)
DFCI ALL Consortium Trials

Induction → CNS Phase → Consolidation → Maintenance

- **Consolidation (week 7)**
  - **Asparaginase: 20-30 weeks**
    - Goal: Maintain continuous asparagine depletion
    - E.coli ASP 25,000 IU/m2/week
      - PEG ASP 2500 IU/m2 every 2 weeks
  - **Vincristine/steroid pulses every 3 weeks**
    - **SR**: weekly methotrexate, daily 6MP
    - **HR**: doxorubicin every 3 weeks
DFCI ALL Consortium Trials (1996-2000)

10-year EFS: 80%
10-year OS: 89%

## DFCI ALL Consortium: Adolescents

- **844 patients treated between 1991-2000**
- **Median follow-up 6.5 years**

<table>
<thead>
<tr>
<th></th>
<th>1-10 yrs</th>
<th>10-14 yrs</th>
<th>15-18 yrs</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>685</td>
<td>108</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>T-cell</td>
<td>7%</td>
<td>14%</td>
<td>29%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC (median)</td>
<td>9,900</td>
<td>10,050</td>
<td>6,500</td>
<td>0.18</td>
</tr>
<tr>
<td>TEL/AML1</td>
<td>28%</td>
<td>24%</td>
<td>0%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>N</td>
<td>685</td>
<td>108</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>IF/ID</td>
<td>6/2</td>
<td>3/1</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>99%</td>
<td>96%</td>
<td>94%</td>
<td>0.01</td>
</tr>
<tr>
<td>Relapse</td>
<td>14%</td>
<td>20%</td>
<td>14%</td>
<td>0.18</td>
</tr>
<tr>
<td>CR Death</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
<td>0.40</td>
</tr>
<tr>
<td>2\textsuperscript{nd} Malig</td>
<td>0.3%</td>
<td>0.9%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>CCR</td>
<td>571 (83%)</td>
<td>82 (76%)</td>
<td>40 (78%)</td>
<td>0.17</td>
</tr>
</tbody>
</table>
# DFCI Consortium: EFS by Age and Phenotype

<table>
<thead>
<tr>
<th>5-year EFS</th>
<th>1-10 yrs</th>
<th>10-14 yrs</th>
<th>15-18 yrs</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-precursor</td>
<td>85 ± 1</td>
<td>75 ± 5</td>
<td>77 ± 7</td>
<td>0.05</td>
</tr>
<tr>
<td>T-ALL</td>
<td>82 ± 5</td>
<td>87 ± 9</td>
<td>79 ± 11</td>
<td>0.88</td>
</tr>
</tbody>
</table>
## Outcome of Older Adolescents by Pediatric Treatment Regimen

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>N</th>
<th>5-year EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFCI 91-01/95-01</td>
<td>1991-2000</td>
<td>51</td>
<td>78%</td>
</tr>
<tr>
<td>CCG 1961</td>
<td>1996-2002</td>
<td>262</td>
<td>68%</td>
</tr>
<tr>
<td>FRALLE 93</td>
<td>1993-1999</td>
<td>77</td>
<td>67%</td>
</tr>
<tr>
<td>BFM 90</td>
<td>1990-1995</td>
<td>141</td>
<td>64%</td>
</tr>
<tr>
<td>DCOG 6-9</td>
<td>1984-1999</td>
<td>47</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>1-10 yrs</td>
<td>10-14 yrs</td>
<td>15-18 yrs</td>
</tr>
<tr>
<td>----------------</td>
<td>----------</td>
<td>-----------</td>
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</tr>
<tr>
<td>N</td>
<td>685</td>
<td>108</td>
<td>51</td>
</tr>
<tr>
<td>Allergy</td>
<td>15%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2%</td>
<td>14%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Barry et al, J Clin Oncol 15:813, 2007
## DFCI Consortium: Asparaginase Toxicity

<table>
<thead>
<tr>
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<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>685</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>15%</td>
<td>10%</td>
<td>0.41</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3%</td>
<td>4%</td>
<td>0.67</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2%</td>
<td>10%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
DFCI Consortium: Other Toxicities

- Infections: No difference by age (p=0.99)
Adolescent Outcome: Summary

• Relatively favorable EFS
  – 15-18 years: 5 yr EFS 78%

• Reasonably well-tolerated
  – Increased risk of:
    • Asparaginase-related TE complications
  – No increased risk:
    • Asparaginase-related pancreatitis or allergy
    • Infections
  – Increased risk of Osteonecrosis in younger adolescents?
    • ?Peak risk from age 10-14 years old
• Could relatively favorable results for adolescents be extended to young adults with ALL?
Protocol 01-175: Adult ALL Pilot

- Pilot of DFCI ALL Consortium Pediatric Regimen in Adults with ALL
- Eligibility
  - Newly diagnosed ALL (excluding mature B-cell)
  - Age 18-50 years
  - No prior chemotherapy
- Objective: Determine feasibility of administering Pediatric DFCI regimen in adults
Protocol 01-175: Adult ALL Pilot Trial

- **Treatment:** same as HR arm of DFCI Childhood ALL Protocol 00-01
  - Including: 30 weeks of E.coli asparaginase during consolidation
  - Note: Ph+ ALL to SCT in 1\textsuperscript{st} CR (imatinib pre-SCT)

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**Induction** → **CNS Phase** → **Consolidation** → **Maintenance**

- **Induction:** 4 weeks
- **CNS Phase:** IT Chemo + XRT
- **Consolidation:** Over a period of 30 weeks
- **Maintenance:** Until 2 years of CCR
Protocol 01-175: Phases of Treatment

- **Remission Induction**: 4 weeks
  - IT-chemo days 1, 15, 29
  - VCR, Pred, Dox, HD-MTX, E.coli ASP x 1, + imatinib if Ph+

- **CNS**: 3 weeks
  - IT-chemo MAH X 4 + 18 Gy Cranial XRT
  - VCR, Dox, 6-MP

- **Consolidation**: 30 weeks
  - VCR/dexamethasone every 3 weeks, standard-dose 6MP
  - Doxorubicin (cumulative dose 300 mg/m²)
  - IT-chemo every 18 weeks
  - Weekly E.coli ASP x 30 weeks

- **Continuation**: until 2 years CCR
  - VCR/dexamethasone every 3 weeks
  - Daily 6MP, weekly MTX (standard dose)
  - IT-chemo q18 weeks
Protocol 01-175: Adult ALL Pilot

- Open for accrual: 2002-2008
- 11 participating sites
- N=94 evaluable patients
Protocol 01-175:
Presenting Characteristics

- Median age: 28 years (range 18-50)
- 61% male, 39% female
- 75% B-precursor, 25% T-cell
- Median WBC at diagnosis: 15.5 K (range 1.0-3600)
- Philadelphia Chromosome: 22%
Protocol 01-175: Summary

- The administration of an asparaginase-intensive pediatric regimen in adults with ALL is feasible, with acceptable toxicity
- Encouraging preliminary EFS/OS
  - This approach *may* lead to better survival rates for adults with ALL
  - Longer follow-up is needed
DFCI Consortium Adult ALL: Follow-up Trial

- Continue to treat adults per DFCI ALL Pediatric Regimen
- Pilot IV PEG asparaginase during consolidation
  - 15 doses given every 2 weeks
Asparaginase dosing in AYA population

- ASP dosed by BSA
  - E.coli ASP 25,000 IU/m²/week
- High interpatient variability in ASP enzyme levels
- ?optimal ASP dose
  - ?optimal dose varies by patient subgroup (age)
Protocol 00-01: Asparaginase Randomization

E.coli L-ASP 25,000 IU/m² IM x 30 weeks

E.coli L-ASP 12,500* IU/m² IM x 30 weeks

ASP levels I I I I I I I I I I I I I I I I

1 2 3 4 5 6 7 8 9 … 30 weeks

*increase/decrease dose to maintain asparagine depletion (Nadir ASP level 0.1-0.14 IU/ml)
Protocol 00-01: ASP Enzyme levels

- Measured every 3 weeks
- Nadir level (1 week after last dose)
- Validated biochemical assay performed in central laboratory
- Lower limit of quantitation: 0.025 IU/mL
- Inter-day Accuracy: 99.7%

Note: Serum asparaginase measurements are “gold standard”, but not performed due to technical limitations
ASP Enzyme Levels

• Asp Enzyme Level ≥ 0.01 IU/mL considered “therapeutic”
  – Previously correlated with serum asparagine depletion
Protocol 00-001

- Open for Accrual: 2000-2005
- 385 randomized patients
  - Fixed: 196
  - Individualized: 189
- Asparaginase samples: 2545 analyzed
Asparaginase Enzyme Levels by Age: Summary

- Fixed Dose Arm: Patients 10-18 years old have higher median nadir ASP levels (7 days after dose of E.coli ASP) compared with younger patients (p<0.01)
- Individualized Dose Arm: Lower median dose in patients 10-18 years old compared to younger patients

Adolescents may achieve adequate ASP depletion with lower doses of asparaginase
AYA ALL: Conclusions

• Biologically higher risk disease
• Relatively favorable outcomes when treated with ASP-intensive pediatric regimen
• Therapy reasonably well-tolerated in AYA patients
  – Increased risk for ASP-related TE complications (pancreatitis)
  – Majority of patients able to tolerate 26+ weeks of ASP
• Pilot trial of DFCI Pediatric Regimen in adults
  – Appears feasible
  – Encouraging preliminary outcome results
• Optimal ASP dose in AYA patients to be determined
  – May be adequately treated with lower doses than younger children
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- St. Justine (Montreal)
- University of Rochester (NY)

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- Ilene Galinsky, RN, NP

DFCI Adult Consortium
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