WORKSHOP C

Staying the Course: Addressing Compliance Challenges in the Treatment of Pediatric Leukemia

Wendy Landier, PhD, CRNP
Mark D. Minden, PhD, MD, FRCPC
Adherence to Oral Chemotherapy in Children with ALL

Wendy Landier PhD CRNP
Phases of Therapy for Pediatric ALL

- **Induction**: 6 - 9 months
- **Consolidation**: 1.5 to 2.5 years
- **Interim Maintenance**: 2 to 3 years
- **Intensification**
- **Maintenance**

Landier & Wallace, 2003
**Maintenance Therapy**

- Longest phase of therapy for pediatric ALL (~1.5 - 2.5 years)
- Relies primarily on oral chemotherapy given at home
How is Adherence Defined?

The ratio of the doses taken to doses prescribed

<table>
<thead>
<tr>
<th>Study</th>
<th>Adherence Assessment</th>
<th>Patients</th>
<th>Non-Adherence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lennard et al. (1995)</td>
<td>6TGN and MMP RBC metabolite levels</td>
<td>327</td>
<td>10%</td>
</tr>
<tr>
<td>Macdougall et al. (1992)</td>
<td>6MP urinary liquid chromatography</td>
<td>39</td>
<td>19%</td>
</tr>
<tr>
<td>Davies et al. (1993)</td>
<td>Interview, 6TGN RBC metabolite levels</td>
<td>35</td>
<td>20%</td>
</tr>
<tr>
<td>Lau et al. (1998)</td>
<td>6MP via MEMS cap (electronic monitoring)</td>
<td>24</td>
<td>33%</td>
</tr>
<tr>
<td>Smith et al. (1979)</td>
<td>Urinary 17-ketogenic steroid level</td>
<td>52</td>
<td>33%</td>
</tr>
<tr>
<td>Tebbi et al. (1986)</td>
<td>Interview, serum corticosterone level</td>
<td>46</td>
<td>40%</td>
</tr>
<tr>
<td>Lansky et al. (1983)</td>
<td>Urinary 17-ketogenic steroid level</td>
<td>31</td>
<td>42%</td>
</tr>
<tr>
<td>Festa et al. (1992)</td>
<td>Serum DHEA-S</td>
<td>21</td>
<td>52%</td>
</tr>
</tbody>
</table>

Suboptimal adherence is clinically prevalent
**6MP Adherence and Risk of Relapse**

<table>
<thead>
<tr>
<th>Adherence to 6MP</th>
<th>Hazard Ratio</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>≥95%</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>94.9% to 90%</td>
<td>4.1</td>
<td>0.02</td>
</tr>
<tr>
<td>89.9% to 85%</td>
<td>4.0</td>
<td>0.04</td>
</tr>
<tr>
<td>&lt;85%</td>
<td>5.7</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Clinically relevant level of adherence

Multivariate analysis

**Missing >1 out of every 20 doses was associated with a significantly increased risk of relapse**
Clinically Relevant Level of Non-Adherence

Using 95% adherence as the cut-point:

- 44% of the study participants were non-adherent
- Non-adherent patients were 2.5-fold more likely to relapse (p=0.002) compared with adherent patients
- The adjusted risk of relapse attributable to non-adherence was 58.8%

Non-adherence (even an occasional missed dose of 6MP) is an important problem

Bhatia et al., 2012
What Factors Influence Adherence?

<table>
<thead>
<tr>
<th>Medication</th>
<th>SIG</th>
<th>Qty</th>
<th>Refills</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial for Do Not Substitute
Please Indicate RX 1 or 2 (circle #s that apply)

☐ Label in Spanish
Factors Associated with Non-Adherence

- Older age (particularly adolescence)
- Male gender
- Single parent family w/multiple children
- Multiple caregivers
- Maternal employment outside the home
- Lower levels of parental education
- Lower socioeconomic status
- Non-white race/ethnicity
- Lack of knowledge/understanding of treatment
- Complexity of treatment regimen

Baker et al., 1993; Festa et al., 1992, Tamaroff et al., 1992; Lennard et al., 1995; Macdougall et al., 1992; Smith et al., 1979; Lancaster et al., 1997; Tebbi et al., 1986; de Oliveira et al., 2004; Landier et al., 2011; Bhatia et al., 2012, 2014
ALL Maintenance Therapy: Complexities
ALL Maintenance Therapy:
Rules about Food

- Corticosteroids:
  - Take with food

- 6MP and Methotrexate:
  - Take on an empty stomach
  - Take 1 hour before or 2 hours after meals
ALL Maintenance Therapy: Rules about Citrus, Milk/Dairy

- **Corticosteroids:**
  - With milk/dairy or preferred liquid

- **6MP and Methotrexate:**
  - Without milk/dairy
  - Without citrus
  - With water
ALL Maintenance Therapy: Rules about Timing

- **Corticosteroids:**
  - Take 2-3 times/day

- **6MP and Methotrexate:**
  - Take once in the evening
ALL Maintenance Therapy: Rules about Timing

- **Corticosteroids**
  - Take for 5 days every month

- **6MP**
  - Take every day

- **Methotrexate**
  - Take once a week
## Oral Maintenance Medications for ALL

BSA = 1.0 m²

<table>
<thead>
<tr>
<th></th>
<th>Mon</th>
<th>Tues</th>
<th>Wed</th>
<th>Thurs</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famotidine</td>
<td>Break</td>
<td>Dinner</td>
<td>Bedtime</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly pill count = 64.5</td>
<td></td>
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</tr>
</tbody>
</table>

### Oral Maintenance Medications for ALL

- **Dexamethasone**
- **TMP-SMX**
- **Famotidine**
- **Breakfast**
- **Dinner**
- **Bedtime**
- **6MP**
- **Methotrexate**

Weekly pill count = 64.5
What are the barriers to and facilitators of adherence to maintenance therapy in pediatric ALL?
A Grounded Theory of the Process of Adherence to Oral Chemotherapy in Hispanic and Caucasian Children and Adolescents With Acute Lymphoblastic Leukemia

Wendy Landier, PhD, RN, CPNP, CPON® ¹, Cynthia B. Hughes, EdD, RN, PNP ², Evelyn R. Calvillo, DNSc, RN ², Nancy L. R. Anderson, PhD, RN, FAAN ³, Deborah Briseño-Toomey, RN, MSN, PNP, CPON® ¹, Leticia Domínguez, BA ¹, Alex M. Martinez, MA ², Cara Hanby, BS ¹, and Smita Bhatia, MD, MPH ¹

Abstract

Children and adolescents with acute lymphoblastic leukemia (ALL) receive treatment that relies on daily self- or parent/caregiver-administered oral chemotherapy for approximately 2 years. Despite the fact that pediatric ALL is uniformly fatal without adequate treatment, nonadherence to oral chemotherapy has been observed in up to one third of patients. Little is known about the reasons for nonadherence in these patients. This study used Straussian grounded theory methodology to develop and validate a model to explain the process of adherence to oral chemotherapy in children and adolescents with ALL. Thirty-eight semistructured interviews (with 17 patients and 21 parents/caregivers) and 4 focused group discussions were conducted. Three stages were identified in the process of adherence: (a) Recognizing the Threat, (b) Taking Control, and (c) Managing for the Duration. Doing Our Part was identified as the core theme explaining the process of adherence and involves the parent (or patient) taking responsibility for assuring that medications are taken as prescribed. Understanding the association between taking oral chemotherapy and control/cure of leukemia (Making the Connection) appeared to mediate adherence behaviors.
Barriers

- No or limited prior illness experience

“He never took medicine before because he was never sick . . . and so that was his first experience. To be honest, he never took Tylenol or anything.”

- Mother of 9-year-old boy
Medication aversion/negative experiences

“It would take us hours to try to get her to do it. And we’d wrap her up like a burrito, and crush it and she’d spit it out. And we’re like, ‘Okay how many pills did she spit out? How much did we give her?’ And by the time we’d finally get her dose in, it was time for the next dose.

It was so horrendous it got to the point where I just said, ‘If you don’t do this you’re gonna die!’ She didn’t care. Because the problem is - Prednisone is the most bitter tasting medicine you can imagine. It was our living nightmare.”

- Mother of 8-year-old girl
Barriers

- Side effects

“He would literally eat and eat and eat. And fruit wouldn’t cut it - they are not craving greens. The doctor said ‘get him some fruit.’ Well that’s not what he wants, it doesn’t work like that - three hot dogs later and he’s asking for something else.”

- Parents of a 2-year-old boy
Barriers

- Side effects

“I took a lot of Prednisone and Decadron...that had really major side-effects like mood swings and things like that - but also like appetite. I was a bottomless pit. I’d cry - I wouldn’t even know why sometimes. I’d get all mad. Sometimes I was like nuts...It was like out of nowhere, no reason - I just started bawling. And then I got even more upset ‘cuz I had no reason, and I was just like, ‘I hate this stuff! I don’t even know why I’m doing this, and I can’t stop crying and I don’t know why, and this medication is insane, and I don’t like it.’”

- 23 year old male diagnosed at age 15
Developmental Considerations

“I was told that she should not take the medication with milk products and that she should not take it with food...and at the time she didn’t have a whole lot of energy and she’d eat, and then she’d fall asleep...So I would wake her up, pull her out of bed, and she’d be tired, and it would take me a really long time to wake her up. And I’d put her in the kitchen and shake her and say ‘you’ve got to take this pill,’ and ‘No, no, I’m not taking it!’ And we’d go in this argument and I’d say ‘Well, you ate and I just can’t give it to you, and you had milk.’ And so finally we’d battle it out and she’d take it, put her right back to sleep and she’d fall asleep. And that was the worst part of my life, because I was up all night.”

- Mother of 3-year-old girl
Barriers

- Not understanding purpose of oral chemotherapy

“I had more pills than I can name or remember… I didn’t remember what any of them were for.”

- 23 year old male diagnosed at age 18
Barriers

- Forgetfulness

“Sometimes I would forget... I would take it, and the following week I wouldn’t take it, I would forget.”

- 15-year-old girl diagnosed at age 12

“There’s times I forgot... the biggest thing was if I’d forgotten my pill box somewhere. Like ‘Oh, I’m out of town for the night’ and this and that. So whatever, usually I’d just take two the next day.”

- 23-year old male, diagnosed at age 15
Facilitators

- Developing pill-swallowing skills
- Overcoming poor palatability
- Anticipatory guidance (side effects/management)
Facilitators

- Learning pill-swallowing

“And then the nurse – she told me that...you take the water bottle, your lips around it, and you swallow – and it goes down right away. Cuz like when you lift your head up like – it all, it goes down – so it’s easier to take. And I did, and I was like ‘Holy cow! This is a piece of cake – this is a lot easier!’”

- 19-year-old boy diagnosed at age 12
Facilitators

- Understanding purpose of medications
- Conveying that medication-taking is not negotiable
- Providing immediate positive reinforcement/rewards (younger children)
- Encouraging longer-term incentive/something to look forward to (older children/teens)
Facilitators

- Understanding purpose of medications

“I would just take it. Even if I did have a side effect, I would just have to deal with it. ‘Cuz I would say “It’s either having this side effect or having an effect that will cost me my life.”

- 14 year old girl diagnosed at age 10
Facilitators

- Understanding purpose of medications

“We drew a picture and we said ‘You have bad cells, and these pills are going to kill the bad cells.’ And he named the pills ‘gunner’ like the gunner in a war. And he really loved that, and it was real helpful to him. And as much as he hated the pills, we could remind him that ‘Your gunner is going to go in and kill.’ And you know, boys - they just are drawn to that- we had no problem with that: ‘Shoot away!’ So definitely there is no way he could have had the commitment he had if he didn’t understand that, I think.”

- Mother of 2-year-old boy
Facilitators

- Conveying that medication-taking is non-negotiable

“And I was a bit tough with her in the sense that I would tell her, ‘You can do it, and if you want to get better you have to do this’….And so it hurt me to be tough with her, strict…and she would get mad at me and I would feel awful. But it was for her own good, even though it hurt me to tell her she had to do it.”

- Mother of 14-year-old girl diagnosed at age 10
Facilitators

- Use of reminders
- “Buddy system”/teamwork
Facilitators

- Reminder systems

“They gave you that calendar... I always looked at it. Even though I thought I knew what I was going to give her, I would always look at it just to be sure.”

- Mother of 14-year-old girl diagnosed at age 10
Facilitators

- “Buddy system”/teamwork

“My mother reminded me to take my pills. She would prep them for me, or she would tell me to prep them, but one or the other of us would make sure that I got my pills.”

- 18 year old female
  diagnosed at age 11

“When it comes to my health – I let my mom butt into my health business, or life – so to speak.”

- 19 year old male
  diagnosed at age 13
ACCL1033: A Comprehensive Approach to Improve Medication Adherence in Pediatric ALL

R01 CA174683; Bhatia, Landier
ACCL1033: Eligibility Criteria

- Age 1-21 years at time of ALL diagnosis
- In first remission
- Currently in the Maintenance phase of therapy receiving continuous oral 6MP
ACCL1033: Study Design

- STUDY ENTRY
- Randomization
  - EDUCATION ONLY
  - INTERVENTION PROGRAM
Education

Select the protocol arm that this patient has been randomized to:
- EDU
- IP

Select the patient’s current age:
- Under Age 12
- Age 12 or Older

Please select the preferred language:
- English
- Español

The world’s childhood cancer experts
Education
Select the patient’s current age:

- **Under Age 12**
- **Age 12 or Older**
Patient Education

Important 6MP Instructions

- Same Time Every Day
- Exactly as Prescribed
- Take in the Evening
- On Empty Stomach
- Take with Water

Maintenance Phase
Success Depends On You
Patient Education

6-MP
Mercaptopurine

[Diagrams of 6-MP and related molecules]
Intervention

6MP Reminders
- Written Instructions
- Cell Phone Reminders
- Parental Supervision

CHILDREN'S ONCOLOGY GROUP
The world's childhood cancer experts
**Intervention: Written Reminders/Texts**

![Image of a patient's medication schedule and a text message reminder](image)

**Peapack General Hospital**

**Mercaptopurine (6MP) Schedule**

<table>
<thead>
<tr>
<th>Time</th>
<th>Wednesday January 4</th>
<th>Thursday January 5</th>
<th>Friday January 6</th>
<th>Saturday January 7</th>
<th>Sunday January 8</th>
<th>Monday January 9</th>
<th>Tuesday January 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00AM</td>
<td>2 Tablets</td>
<td>1 Tablet</td>
<td>2 Tablet</td>
<td>1½ Tablet</td>
<td>2 Tablet</td>
<td>1½ Tablet</td>
<td>2 Tablet</td>
</tr>
<tr>
<td>Week 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Wednesday January 11</td>
<td>Thursday January 12</td>
<td>Friday January 13</td>
<td>Saturday January 14</td>
<td>Sunday January 15</td>
<td>Monday January 16</td>
<td>Tuesday January 17</td>
</tr>
<tr>
<td>9:00AM</td>
<td>1½ Tablet</td>
<td>2 Tablet</td>
<td>1½ Tablet</td>
<td>2 Tablet</td>
<td>1½ Tablet</td>
<td>2 Tablet</td>
<td>1½ Tablet</td>
</tr>
</tbody>
</table>

**Text Message**

Jane: Take 6MP, 2 tablets at 9:30 PM. Text “1” when you have taken your 6MP. Thank you. Robert Smith MD.
Intervention: Parental Supervision
Summary

- ALL maintenance therapy in pediatrics is:
  - Crucial
  - Complex

- Non-adherence to oral chemotherapy is common
  - Almost half of patients do not attain an optimal level of adherence
Barriers to adherence include:
- Forgetfulness
- Lack of understanding

Facilitators of adherence include:
- Using a reminder system
- “Buddy system”/teamwork
- Understanding importance of oral chemotherapy
WORKSHOP C

Staying the Course: Addressing Compliance Challenges in the Treatment of Pediatric Leukemia

Wendy Landier, PhD, CRNP
Mark D. Minden, MD, PhD, FRCPC
AYA Protocols in Ontario

• Modified Dana Farber Cancer Institute
• Hyper-CVAD
Modified Dana Farber

- Induction phase-28 days in hospital
- CNS phase-three weeks
- Intensification Phase-30 weeks
- Maintenance Phase-to two years
CNS Phase

- IT chemo twice a week for two weeks
- Doxorubicin
- Vincristine
- 6 MPx14 days qhs
Intensification Phase

• Q3wk schedule
• Doxorubicin-IV day 1-cycle 1-7
• Vincristine-IV day 1
• Dexamethasone BIDx5d
• 6MP d1-14 qhs
• Asparaginase weekly x 30 wks
• Methotrexate-day after Asnase cycle 8-10
Maintenance Phase

• Q3wk schedule
• Vincristine weekly
• Dexamethasone BIDx5d
• 6MP d1-14 qhs
• Methotrexate IV/IM weekly
Patient’s Highly Engaged

The IM methotrexate is done through home care/CCAC. This requires using a third computer program and fax machine. Occasionally Dr. Minden misses one of the steps and the patient or partner will call to ask where there MTX order is.
Key Aspects

• Close association with care team-ie q3wk or more often
• MTX is IV or IM
• Drug dosing has a neutrophil target
HyperCVAD

• Four A and B cycles-each q3wk
• Maintenance to 2 years-same as DFCI
A Cycle

- Cyclophosphamide q12h x 3 days
- Vincristine d 4 and 11
- Doxorubicin d 4
- Dexamethasone d 1-4 and d 11-14
- Asparaginase d 4 and 11
B cycle

- High dose methotrexate d 1
- High dose cytarabine d 2 and 3 q12h