Lack of consensus on type and duration of immunosuppressive medication use in SCT

Post-Tx day of immunosuppression tapering initiation in GVHD-free patients

Survey in 220 physicians, using case vignets

Overview of presentation

1. Definition of medication nonadherence
2. How frequently does it occur?
3. What are the consequences?
4. What are possible risk factors?
5. What are the implications for SCT?
Medication adherence taxonomy

ADHERENCE: “the extent to which the person’s behavior (taking medications, following a recommended diet and/or executing lifestyle changes) corresponds with the agreed recommendations from a health care provider.”

ADHERENCE = “the extent to which the person’s behavior (taking medications, following a recommended diet and/or executing lifestyle changes) corresponds with the agreed recommendations from a health care provider.”

Implementation of SCT treatment

TAKING

+ DOISING

+ TIMING

+ DRUG HOLIDAYS

Examples of implementation patterns (kidney Tx)

Dot= dose taken; bar= missed dose

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Prevalence of non-initiation

Prevalence of no fill, primary, or initial nonadherence in 20 studies (various diseases and treatments):
2.3 – 50% (weighted average: 5.1 ± 1.3)

Prevalence of “non-initiation” in 151 adult patients undergoing outpatient autologous SCT

- Nonadherence assessed through retrospective chart review
- Examples of nonadherence: non-executing self-care behaviors (e.g., oral care, hygiene), refusing medications or not exercising
- Overall percentage of non-initiation:

\[
\frac{\text{total number of nonadherent days}}{\text{total length of stay in days}} = 16.6\% (SD= 15.6)
\]

Prevalence of implementation problems in chronic illness and adult solid organ Tx patients

Mean nonadherence/non-implementation across 17 illnesses: 20.6%

Meta-analysis
- 22.6 per 100 cases/year
- Kidney transplantation highest risk
- 37 per 100 cases/year

Type of adult transplantation

**Prevalence of implementation problems in pediatric solid organ transplant patients**

- Adolescent kidney Tx: 42.8%
- Pediatric kidney Tx: 24.3%

**Implementation and persistence problems in 376 allogeneic SCT survivors (PROVIVO study)**

<table>
<thead>
<tr>
<th>Adherence dimension</th>
<th>Immunosuppressive medication (N= 95 / 376)</th>
<th>Other medication (N= 170 / 376)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMPLEMENTATION PROBLEMS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking NA (missed ≥ 1 dose in last month)</td>
<td>33 (33.3%)</td>
<td>64 (37.6%)</td>
</tr>
<tr>
<td>Timing NA (&gt; 2 hours from prescribed timing)</td>
<td>61 (61.2%)</td>
<td>-</td>
</tr>
<tr>
<td>Reducing dose on own initiative</td>
<td>4 (4.1%)</td>
<td>12 (7.3%)</td>
</tr>
<tr>
<td>Drug holidays (missing ≥ 2 consecutive doses)</td>
<td>3 (3.2%)</td>
<td>20 (12%)</td>
</tr>
<tr>
<td><strong>NON-PERSISTENCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-persistence</td>
<td>3 (3.2%)</td>
<td>4 (2.4%)</td>
</tr>
<tr>
<td><strong>OVERALL NONADHERENCE</strong></td>
<td>65.7%</td>
<td>-</td>
</tr>
</tbody>
</table>

*Patients were a median of 7.1 years post-transplant (range 1-33 years)*

**Weekly % of electronically monitored doses taken by 6 adolescents after HSCT**

- Fluconazole
- Acyclovir
- Cyclosporine
- Cyclosporine
- Voriconazole

*Patients took on average 73% of their doses (SD= 13%) (range 55-92%) + implementation problems seem to increase over time*
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Good medication adherence (implementation) reduces mortality in chronic illnesses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall mortality rate (%)</th>
<th>Nonadherent (%)</th>
<th>Adherent (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart TX</td>
<td>1.5</td>
<td>3.5</td>
<td>1.5</td>
<td>2.56 (1.03, 6.16)</td>
</tr>
<tr>
<td>Renal TX</td>
<td>2.0</td>
<td>4.5</td>
<td>2.0</td>
<td>2.56 (1.03, 6.16)</td>
</tr>
<tr>
<td>Liver TX</td>
<td>2.5</td>
<td>5.5</td>
<td>2.5</td>
<td>2.56 (1.03, 6.16)</td>
</tr>
</tbody>
</table>

Clinical consequences of implementation problems in solid organ Tx

Late acute rejections

Overall, nonadherent patients have a 2.56 higher odds of experiencing a late acute rejection episode.

Graft loss / mortality

* Weighted mean

(Dobbins et al. Work in progress)
(Russell et al. B-Serious systematic review, paper in progress)
Minimal deviations from prescribed regimen already sufficient to result in poor outcomes

**Implementation problems in first 3 years after kidney transplantation based on Medication possession ratio (N= 15 252)**

<table>
<thead>
<tr>
<th></th>
<th>GRAFT FAILURE</th>
<th>DEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Excellent (&gt;99.9%)</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>Good (95.1-99.8%)</td>
<td>1.12 (0.92-1.36)</td>
<td>0.25</td>
</tr>
<tr>
<td>Fair (81.1-95%)</td>
<td>1.63 (1.37-1.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Poor (&gt; 81%)</td>
<td>1.80 (1.52-2.13)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Guidance on minimal level of implementation required in solid organ Tx:**
At least 95% taking + deviation in timing of < 2 hours

(Finkley et al. Am J Transplant 2006; 6: 2597-2604)

---

Pre-Tx medication nonadherence predictive for post-transplant outcomes (N= 117)

<table>
<thead>
<tr>
<th>0%</th>
<th>40% suboptimal adherence</th>
<th>60% good adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missed med</td>
<td>↑ cost of non-taken medication</td>
<td></td>
</tr>
<tr>
<td>FK57 initial dose</td>
<td>↑ cost for treatment of morbidity</td>
<td></td>
</tr>
<tr>
<td>FK57 final dose</td>
<td>↑ cost of avoidable hospitalizations</td>
<td></td>
</tr>
</tbody>
</table>

(Foster et al. Bone Marrow Transplant 2008; 44: 375–380)

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**Economic consequences**

**Direct costs**
- ↑ cost of non-taken medication
- ↑ cost for treatment of morbidity
- ↑ cost of avoidable hospitalizations

**Indirect costs**
- Missed schooldays / work days
- Cost for transportation, household, child care
- ↓ quality of life
- ↑ cost of evolving more potent medications
Cost of poor implementation in adult kidney Tx (15 525 adult US patients)

21 600$ higher adjusted cost at 3 years

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Understanding the drivers of nonadherence: a multi-faceted problem

Socio-economic
Healthcare system-related
Condition-related
Patient-related
Treatment-related

Sabate, World Health Organization 2003
Examples of correlates / risk factors

<table>
<thead>
<tr>
<th>Socio-economic</th>
<th>Condition related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor socio-economic status</td>
<td>Depression</td>
</tr>
<tr>
<td>Low education/literacy</td>
<td>Cognitive problems</td>
</tr>
<tr>
<td>Cost of medication</td>
<td>Higher co-morbidity</td>
</tr>
</tbody>
</table>

**PROBLEMS:**
- Lack of prospective studies
- Lack of a theory-based approach (shooting from the hip approach)
- Suboptimal measurement methods
- Arbitrary operational definition of nonadherence

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Health beliefs/attitudes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of daily doses</td>
<td>Forgetfulness</td>
</tr>
<tr>
<td>Frequent changes in medications</td>
<td>Busy lifestyle</td>
</tr>
</tbody>
</table>

**Most nonadherence is non-intentional!!!!**

Healthcare system related factors related to nonadherence in chronic myeloid leukemia

- Having received less information or lower satisfaction with information received
- Feeling not being involved in decision making process
- Poor patient-physician relationship
- Median duration of follow-up visits
- Years of experience / seeing less patients with CML
- Less frequent contacts with same hematologist (lack of continuity of follow-up)
- Poor access to the treating clinic
- Medication not available at pharmacy

Results of a meta-analysis on physician communication

1) Odds of adherence 2.16 times higher if physician is good communicator
2) Odds of adherence 1.62 times higher if physicians received training specifically on adherence communication

The importance of adherence communication skills in clinicians

(Zolnierek et al. Med Care 2009; 47: 826-834)
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A proposed chronic care model

Successful interventions are usually complex and use combined interventions targeting all relevant risk factors (education alone not sufficient)

Assessment of adherence & determinants

Education
Psychological
Behavioral strategies
Prepared patients to self-manage medications

One size does not fit all: tailored ongoing support is needed (interventions should be sustained over time)

Overview of most frequently used interventions by 143 nurses working in SCT (29 interventions)

<table>
<thead>
<tr>
<th>INTERVENTION (only interventions used by &gt;40% shown)</th>
<th>% used frequently</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHERENCE ASSESSMENT / SCREENING METHODS (3 items)</td>
<td></td>
</tr>
<tr>
<td>Questioning about medication adherence during follow-up visits</td>
<td>67.8%</td>
</tr>
<tr>
<td>Screening patients for risk factors for NA during follow-up</td>
<td>44.8%</td>
</tr>
<tr>
<td>EDUCATIONAL / COGNITIVE INTERVENTIONS (6 items)</td>
<td></td>
</tr>
<tr>
<td>Providing reading materials</td>
<td>79%</td>
</tr>
<tr>
<td>Providing printed medication instructions</td>
<td>58.7%</td>
</tr>
<tr>
<td>Providing individual patient/family teaching</td>
<td>56.6%</td>
</tr>
<tr>
<td>BEHAVIORAL / COUNSELING INTERVENTIONS (11 items)</td>
<td></td>
</tr>
<tr>
<td>Inpatient training of patients on how to take medications</td>
<td>66.4%</td>
</tr>
<tr>
<td>AFFECTIVE / SOCIAL INTERVENTIONS (9 items)</td>
<td></td>
</tr>
<tr>
<td>Involving family/support persons in interventions</td>
<td>51%</td>
</tr>
<tr>
<td>Establishing partnership with patient and significant other</td>
<td>40%</td>
</tr>
<tr>
<td>Providing telephone assistance if needed</td>
<td>44.3%</td>
</tr>
</tbody>
</table>

(Kirsch et al. Eur J Cancer Care 2014; 23: 607-615)
A proposed chronic care model

Involving caregivers as partners in the care process + valuing the role of patient organisations

Involvement of caregivers

Assessment of adherence & determinants

Education

Psychological

Behavioral strategies

Prepared patients to self-manage medications

Trained health professionals

Adherence management should be part of core curriculum of all health professionals

A proposed chronic care model

Ensuring continuity of care along and within settings

Use of community services

Involvement of caregivers

Assessment of adherence & determinants

Education

Psychological

Behavioral strategies

Prepared patients to self-manage medications

Trained health professionals

Healthcare setting that adopts chronic illness care model

Delivery system redesign

The relevance of interdisciplinary care as part of delivery system redesign

Adherence management should be an integral part of long-term follow-up

physicians

Psychologist

Social worker

Patient & caregivers

nurses

Physiotherapist

Dietician

Need for new specialized functions + clinical information systems
**Take home messages**

- Limited evidence suggests that nonadherence is a major problem in SCT, yet its impact on outcome remains unknown.

- There is room for more adherence-related research.

- Adherence management should become part of the core curriculum of all health professionals.

- Adherence and its risk factors should be regularly assessed as part of routine follow-up.

- Interventions should target both the patient and the healthcare system.