A Review of Guidelines and Evidence for the Use of Irradiated Blood Products in Solid Tumor, Chemotherapy Patients

Chris Kim
11/29/12
Background

- Prevention of TAGVHD
- Irradiation: induces DNA crosslinks, prevents (dividing) lymphocyte proliferation
- Dose to the center of the irradiation field must be at least 25 Gy
- Minimum delivered dose delivered to any other portion must be 15 Gy
- No more than 50 Gy
Primary Risk Factors for TA-GVHD

- Degree of recipient immunodeficiency
- Number of viable T cells in the transfusion
- Degree of a population’s genetic diversity
Clinical Scenario

• New blood bank intern gets paged

78123 Please call. Re: 1 UNIT PRBC FOR PT MRN: 555-12-34
H&P

- "31 yo w/ known hx of seminoma and retroperitoneal mass s/p recent BEP, with multiple chemotherapy related complications, including Klebsiella bacteremia and neutropenic fever, presenting with concern for sepsis and neutropenia"
Clinical Scenario

"Are you sure?...you want to give this patient non-irradiated blood?"

“No I am not sure. I’ll call you back!”
• Chemotherapy
  – “On request”
UptoDate Indications for Irradiation

Currently Accepted Indications

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised hematopoietic stem cell recipients or organ transplant recipients</td>
</tr>
<tr>
<td>Patients with hematologic disorders who will be undergoing marrow transplantation imminently</td>
</tr>
<tr>
<td>Intrauterine transfusion</td>
</tr>
<tr>
<td>Neonatal exchange transfusions</td>
</tr>
<tr>
<td>Premature, low birthweight neonates</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Congenital cell-mediated immunodeficiencies</td>
</tr>
<tr>
<td>Thymic hypoplasia (DiGeorge syndrome), Wiskott-Aldrich syndrome, Leiner's disease, 5' nucleotidase deficiency</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia (CLL) patients or other patients receiving fludarabine</td>
</tr>
<tr>
<td>Recipients of directed donations from biologic relatives</td>
</tr>
<tr>
<td>Recipients of donation from HLA-matched donors</td>
</tr>
<tr>
<td>Recipients who are heterozygous at an HLA locus for which the donor is homozygous and shares an allele; most common in genetically homogeneous populations</td>
</tr>
</tbody>
</table>

Probably Indicated

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic malignancies other than Hodgkin lymphoma</td>
</tr>
<tr>
<td>Solid tumors treated with cytotoxic agents</td>
</tr>
</tbody>
</table>
Standards for Blood Banks and Transfusion Services

- 5.17.3 Irradiation - The blood bank for transfusion service shall have a policy regarding the transfusion of irradiated components

- At a minimum, cellular components shall be irradiated when:
  1. A patient is identified as being at risk for TAGVHD
  2. The donor of the component is a blood relative of the recipient
  3. The donor is selected for HLA compatibility, by typing or crossmatching.
Clinical Indications for Irradiated Components

• **Well-documented indications**
  – Intrauterine transfusions
  – Premature, low-birthweight infants
  – Newborns with erythroblastosis fetalis
  – Congenital immunodeficiencies
  – Hematologic malignancies or solid tumors (neuroblastoma, sarcoma, Hodgkin disease)
  – Components that are crossmatched, HLA matched, or directed donations
  – Fludarabine therapy
  – Granulocyte components
Clinical Indications for Irradiated Components

• Potential indications
  – Other malignancies, including those treated with cytotoxic agents
  – Donor-recipient pairs from genetically homogenous populations

• Usually not indicated
  – Patients with human immunodeficiency virus
  – Term infants
  – Nonimmunosuppressed patients
The following were searched systematically for publications in English, until June, 2009

- PubMed - from 1950
- Medline - from 1950
- EMBASE - from 1980
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) - from 1982
- The Cochrane Library 2008, Issue 3
- DARE CRD Website (Centre for Reviews and Dissemination)
- SRI (Systematic Review Initiative) Handsearch Databases

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**Table I: Grades of Recommendations**

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Clarity of Risk/Benefit</th>
<th>Methodological strength of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Clear</td>
<td>Randomised controlled trials without important limitations</td>
<td>Strong recommendation; can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1C</td>
<td>Clear</td>
<td>No randomised controlled trials but strong results from randomised controlled trials can be unequivocally extrapolated, or overwhelming evidence from observational studies</td>
<td>Strong recommendation; can apply to most patients in most circumstances</td>
</tr>
<tr>
<td>1B</td>
<td>Clear</td>
<td>Randomised controlled trials with important limitations (inconsistent results, methodological flaws)</td>
<td>Strong recommendations; likely to apply to most patients</td>
</tr>
<tr>
<td>1C</td>
<td>Clear</td>
<td>Observational studies</td>
<td>Intermediate-strength recommendation; may change when stronger evidence is available</td>
</tr>
<tr>
<td>2A</td>
<td>Unclear</td>
<td>Randomised controlled trials without important limitations</td>
<td>Intermediate-strength recommendation; best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>2C</td>
<td>Unclear</td>
<td>No randomised controlled trials but strong results from randomised controlled trials can be unequivocally extrapolated, or overwhelming evidence from observational studies</td>
<td>Weak recommendation; best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>2B</td>
<td>Unclear</td>
<td>Randomised controlled trials with important limitations (inconsistent results, methodological flaws)</td>
<td>Weak recommendation; alternative approaches likely to be better for some patients under some circumstances</td>
</tr>
<tr>
<td>2C</td>
<td>Unclear</td>
<td>Evidence obtained from respected authorities or from expert committee reports or opinion of the group of experts responsible for these recommendations</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>
Patients who are on “very immune suppressive” chemotherapy

• G1B Recommendation
  – Patients treated with purine analogue drugs (fludarabine, cladribine and deoxycoformicin) should receive irradiated blood components indefinitely
Transfusion-associated GVHD after fludarabine therapy in a patient with systemic lupus erythematosus


<table>
<thead>
<tr>
<th>Reference</th>
<th>Unique patient number</th>
<th>Diagnosis*</th>
<th>Age (years)</th>
<th>Prior therapy</th>
<th>Cycles of fludarabine</th>
<th>Implicated component</th>
<th>Interval between flu and GVHD</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maung et al., 1994</td>
<td>1</td>
<td>B-CLL</td>
<td>61</td>
<td>chlorambucil</td>
<td>1</td>
<td>RBCs</td>
<td>NS</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>B-CLL</td>
<td>47</td>
<td>chlorambucil</td>
<td>4</td>
<td>NS</td>
<td>1 month</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>B-CLL</td>
<td>59</td>
<td>chlorambucil</td>
<td>4</td>
<td>NS</td>
<td>NS</td>
<td>Death</td>
</tr>
<tr>
<td>Briz et al., 1995</td>
<td>4</td>
<td>B-CLL</td>
<td>61</td>
<td>chlorambucil</td>
<td>6</td>
<td>6 U RBCs</td>
<td>Several months</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>COP, CHOP†</td>
<td></td>
<td>6 U PC‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williamson et al., 1996</td>
<td>5</td>
<td>B-CLL</td>
<td>62</td>
<td>COP, CHOP</td>
<td>4</td>
<td>PC</td>
<td>11 months</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>B-CLL</td>
<td>59</td>
<td>chlorambucil</td>
<td>5</td>
<td>RBCs</td>
<td>10 days</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>B-CLL</td>
<td>64</td>
<td>chlorambucil</td>
<td>2</td>
<td>PC</td>
<td>1 month</td>
<td>Death</td>
</tr>
<tr>
<td>Deane et al., 1997</td>
<td>8</td>
<td>AML</td>
<td>20</td>
<td>daunorubicin</td>
<td>3</td>
<td>NS</td>
<td>NS</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AraC, TG§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zelig et al., 1999</td>
<td>9</td>
<td>B-NHL</td>
<td>67</td>
<td>CHOP, XRT¶</td>
<td>4</td>
<td>2 U RBCs</td>
<td>Several months</td>
<td>Death</td>
</tr>
</tbody>
</table>

* B-CLL = B-cell chronic lymphocytic leukemia; AML = acute myelogenous leukemia; B-NHL = B-cell non-Hodgkin's lymphoma.
† COP = cyclophosphamide, vincristine, prednisone; CHOP = cyclophosphamide, vincristine, doxorubicin, prednisone.
‡ PCs = platelet concentrates.
§ AraC = cytosine arabinoside; TG = thioguanine.
¶ XRT = radiation therapy.
Patients who are on “very immune suppressive” chemotherapy

- G2C Recommendation
  - The situation with other purine antagonists such as bendamustine and clofarabine is unclear, but use of irradiated blood components is recommended as these agents have a similar mode of action.
  - Irradiated blood components indicated after alemtuzumab (anti-CD52) therapy.
  - Use of irradiated blood components after rituximab (anti-CD20) is not recommended at this time
Solid Tumors

• Grade 2C Recommendation
  – It is not necessary to irradiate blood components for [patients] with solid tumors

• “Occasional cases of TA-GVHD have been reported after treatment of a variety of solid tumors. This is clearly a rare occurrence. However, the effect of dose escalation of chemotherapy regimens in children and young adults is unknown and should be monitored”
Fatal Graft Versus Host Disease Following a Blood Transfusion in a Child with Neuroblastoma

William G. Woods, MD, and Bertram H. Lubin, MD

From the Hematology Group, Children's Hospital Medical Center, Oakland, California

ABSTRACT. A 2-year-old boy who was receiving intensive chemotherapy for advanced neuroblastoma developed fatal graft versus host disease following administration of a unit of packed red blood cells from an unrelated donor. Graft versus host disease was documented by demonstrating human leukocyte antigen identity between the transfusion donor and the patient's peripheral circulating lymphocytes. Nonirradiated packed red blood cells contain viable lymphocytes and pose a risk to the immunosuppressed cancer patient. Pediatrics 67:217-221,

<table>
<thead>
<tr>
<th>Individual Tested</th>
<th>HLA Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient pre-GVHD</td>
<td>Not performed</td>
</tr>
<tr>
<td>Patient's mother</td>
<td>A2, AW24, B40, BW50</td>
</tr>
<tr>
<td>Patient's father</td>
<td>Deceased</td>
</tr>
<tr>
<td>Blood donor 1</td>
<td>A1, AW24, B8, BW44</td>
</tr>
<tr>
<td>Blood donor 2</td>
<td>A3, X, B7, BW35</td>
</tr>
<tr>
<td>Patient during GVHD</td>
<td>A3, X, B7, BW35</td>
</tr>
</tbody>
</table>

* Abbreviations used are: HLA, human leukocyte antigen; GVHD, graft versus host disease.
A 17-year-old girl diagnosed as having alveolar rhabdomyosarcoma in the right crus that was metastasized to the left breast

- began to be treated with VAC (vincristine, actinomycin D and cyclophosphamide) \(\rightarrow\) (vincristine, doxorubicin and cyclophosphamide) \(\rightarrow\) high dose ifosfomide
- Radiation to Thymus?
  - T cell ‘impairment of the immune system’?
- No HLA typing done
- Turkey - where multiple case reports of TAGVHD arising due to lack of HLA diversity
Fatal transfusion-associated graft-versus-host disease in an immunocompetent recipient of a volunteer unit of red cells

Darrell Triulzi, Rene Duquesnoy, Lawrence Nichols, Kenneth Clark, Drazen Jukic, Adriana Zeevi, and Dennis Meisner

<table>
<thead>
<tr>
<th>Patient</th>
<th>A 1,2</th>
<th>B 8,44</th>
<th>C 7, 5/8</th>
<th>BW 6,4</th>
<th>DRB1 15,17</th>
<th>DRB3 51,52</th>
<th>DQB1 6,3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td>A 1</td>
<td>B 8</td>
<td>C 7</td>
<td>BW 6</td>
<td>DRB1 17</td>
<td>DRB3 52</td>
<td>DQB1 2</td>
</tr>
</tbody>
</table>

Dad | Mom

Child 1 | Child 2 | Child 3 | Child 4

Donor | Recipient

Child 1 | Child 2
Chemotherapy Agents: BEP
  – Bleomycin: Glycopeptide
  – Etoposide: Topoisomerase inhibitor
  – Platinum: Cross link DNA $\rightarrow$ apoptosis
Lab Values

- CBC & PLT & DIFF
- WHITE BLOOD CELL COUNT * 0.59 x10E3/uL
- RED BLOOD CELL COUNT @ 2.89 x10E6/uL
- HEMOGLOBIN @ 8.3 g/dL 13.5-17.1
- HEMATOCRIT @ 23.9 % 38.5-52.0
- MEAN CORPUSCULAR VOLUME 82.7 fL

ABSOLUTE NEUTROPHIL * 0.2 x10E3/uL 1.8-6.9
ABSOLUTE LYMPHOCYTE COUNT @ 0.2 x10E3/uL 1.3-3.4
Cons of Irradiated Products

- Reduced shelf life 35->28 days
- Leakage of potassium
- Theoretical risks
  - Malignant change? Reactivation of latent virus? Plastic leakage?

- Practical issues
  - Tech time (5 minutes)
  - Cost/upkeep/validation/security of irradiators
Potential hazards of irradiation?

• Radiation-induced malignant change
  – It is likely that the dose of gamma irradiation delivered to blood components significantly exceeds the lethal dose for such cells at high dose rates (3-4 Gy min⁻¹), resulting in complete cell death rather than transformation.
Leakage of plasticizer?

- Leakage of plasticiser from the transfusion pack is a theoretical risk for recipients of largevolume transfusions of irradiated components (Rock et al; 1988), particularly for neonates. The effect of irradiation on the many new plastics and plasticizers potentially used in the manufacture of blood packs requires evaluation and monitoring.
Conclusions

As new potent immunosuppressive drugs and biological agents are introduced into practice, there is a need for regular review of recommendations regarding irradiated blood components.