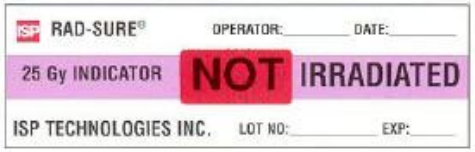
A Review of Guidelines and Evidence for the Use of Irradiated Blood Products in Solid Tumor, Chemotherapy Patients

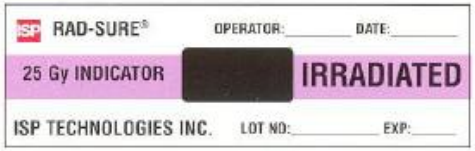
Chris Kim
11/29/12

Background

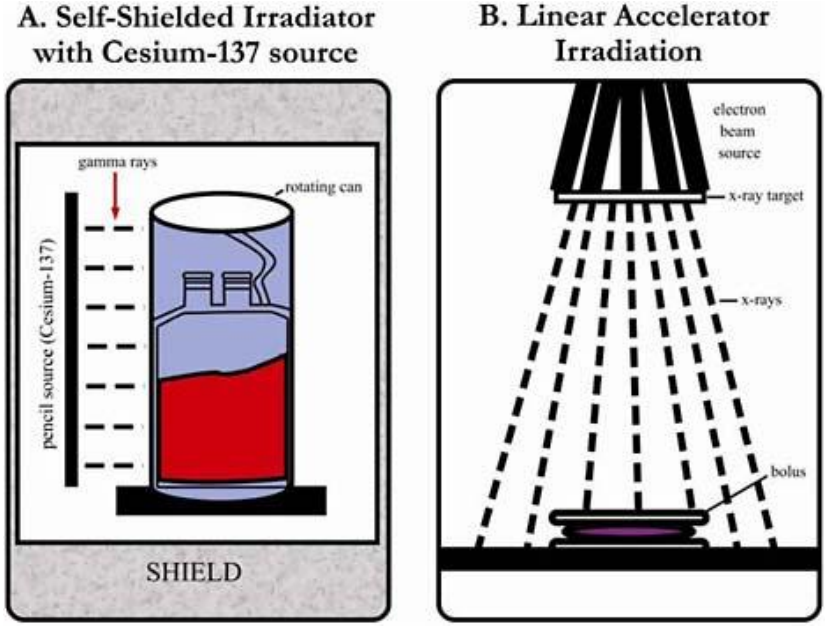
- Prevention of TAGVHD
- Irradiation: induces DNA crosslinks, prevents (dividing) lymphocyte proliferation
- Dose to the center of the irradiation field must be at least 25 Gy
- Minimum delivered dose delivered to any other portion must be 15 Gy
- No more than 50Gy



BEFORE IRRADIATION



AFTER IRRADIATION @ 25 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

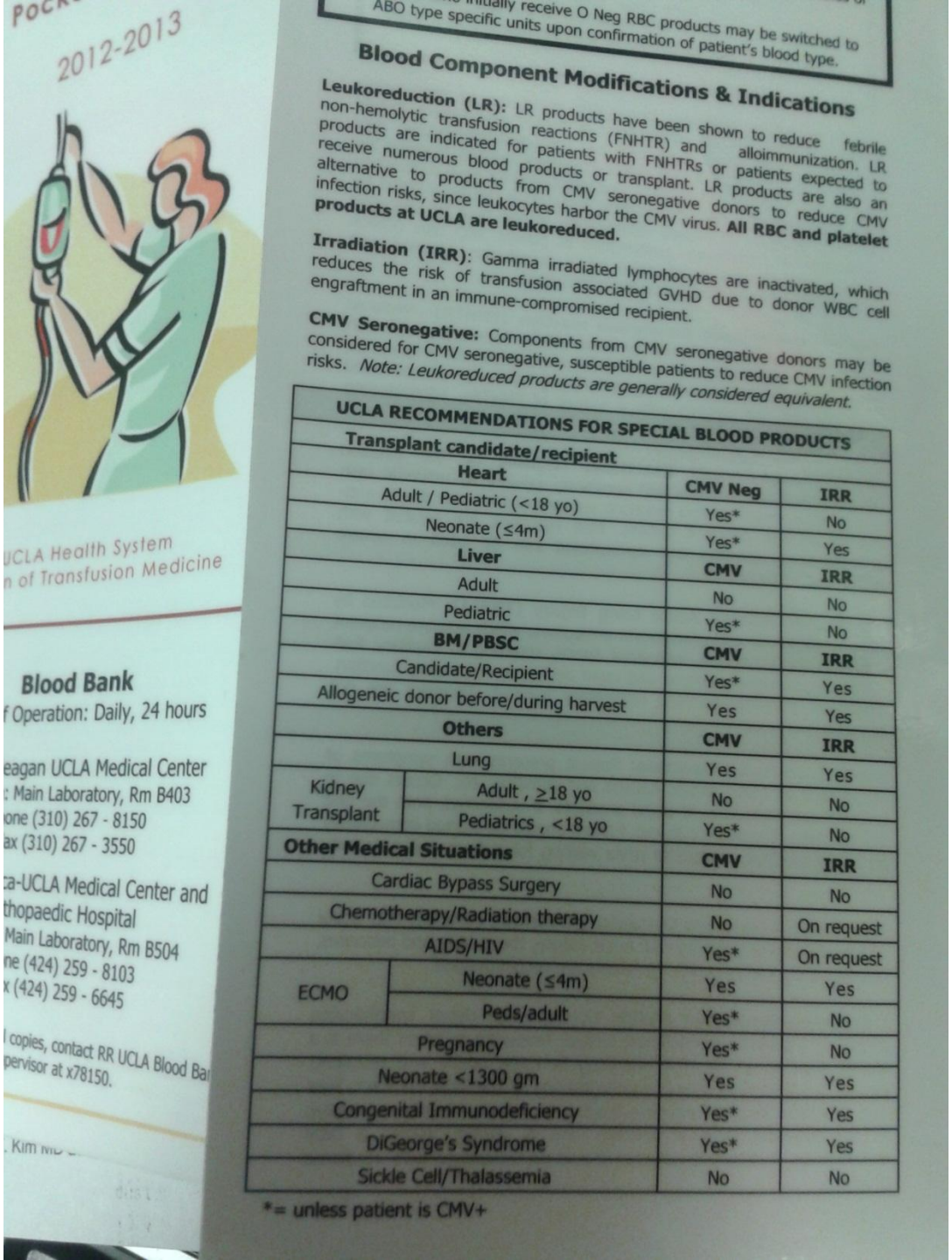
- "31 yo w/ known hx of **seminoma** and retroperitoneal mass s/p recent **BEP**, with multiple chemotherapy related complications, including Klebsiella bacteremia and **neutropenic fever**, presenting with concern for sepsis and neutropenia"

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"



2012-2013

UCLA Health System
n of Transfusion Medicine

Blood Bank
f Operation: Daily, 24 hours

eagan UCLA Medical Center
: Main Laboratory, Rm B403
one (310) 267 - 8150
ax (310) 267 - 3550

ca-UCLA Medical Center and
thopaedic Hospital
Main Laboratory, Rm B504
ne (424) 259 - 8103
x (424) 259 - 6645

l copies, contact RR UCLA Blood Ba
pervisor at x78150.

. Kim MD

initially receive O Neg RBC products may be switched to ABO type specific units upon confirmation of patient's blood type.

Blood Component Modifications & Indications

Leukoreduction (LR): LR products have been shown to reduce febrile non-hemolytic transfusion reactions (FNHTR) and alloimmunization. LR products are indicated for patients with FNHTRs or patients expected to receive numerous blood products or transplant. LR products are also an alternative to products from CMV seronegative donors to reduce CMV infection risks, since leukocytes harbor the CMV virus. **All RBC and platelet products at UCLA are leukoreduced.**

Irradiation (IRR): Gamma irradiated lymphocytes are inactivated, which reduces the risk of transfusion associated GVHD due to donor WBC cell engraftment in an immune-compromised recipient.

CMV Seronegative: Components from CMV seronegative donors may be considered for CMV seronegative, susceptible patients to reduce CMV infection risks. *Note: Leukoreduced products are generally considered equivalent.*

UCLA RECOMMENDATIONS FOR SPECIAL BLOOD PRODUCTS			
Transplant candidate/recipient			
Heart		**CMV Neg**	**IRR**
Adult / Pediatric (<18 yo)		Yes*	No
Neonate (≤4m)		Yes*	Yes
Liver		**CMV**	**IRR**
Adult		No	No
Pediatric		Yes*	No
BM/PBSC		**CMV**	**IRR**
Candidate/Recipient		Yes*	Yes
Allogeneic donor before/during harvest		Yes	Yes
Others		**CMV**	**IRR**
Lung		Yes	Yes
Kidney Transplant	Adult , ≥18 yo	No	No
	Pediatrics , <18 yo	Yes*	No
Other Medical Situations		**CMV**	**IRR**
Cardiac Bypass Surgery		No	No
Chemotherapy/Radiation therapy		No	On request
AIDS/HIV		Yes*	On request
ECMO	Neonate (≤4m)	Yes	Yes
	Peds/adult	Yes*	No
Pregnancy		Yes*	No
Neonate <1300 gm		Yes	Yes
Congenital Immunodeficiency		Yes*	Yes
DiGeorge's Syndrome		Yes*	Yes
Sickle Cell/Thalassemia		No	No

*= unless patient is CMV+

UptoDate Indications for Irradiation

Currently Accepted Indications
Immunocompromised hematopoietic stem cell recipients or organ transplant recipients
Patients with hematologic disorders who will be undergoing marrow transplantation imminently
Intrauterine transfusion
Neonatal exchange transfusions
Premature, low birthweight neonates
Hodgkin lymphoma
Congenital cell-mediated immunodeficiencies
Thymic hypoplasia (DiGeorge syndrome), Wiskott-Aldrich syndrome, Leiner's disease, 5' nucleotidase deficiency
Chronic lymphocytic leukemia (CLL) patients or other patients receiving fludarabine
Recipients of directed donations from biologic relatives
Recipients of donation from HLA-matched donors
Recipients who are heterozygous at an HLA locus for which the donor is homozygous and shares an allele; most common in genetically homogeneous populations
Probably Indicated
Hematologic malignancies other than Hodgkin lymphoma
Solid tumors treated with cytotoxic agents

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 compatability, by typing or crossmathing.

AABB, 27th Edition

AABB Technical Manual

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

AABB Technical Manual

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

Guidelines on the Use of Irradiated Blood Components

Prepared by the BCSH Blood Transfusion Task Force

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

Table I- Grades of Recommendations

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

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

Susan F. Leitman, John F. Tisdale, Charles D. Bolan, Mark A. Popovsky, John H. Klippel, James E. Balow, Dimitrios T. Boumpas and Gabor G. Illei

TABLE 1. Prior reports of TA-GVHD in association with fludarabine therapy

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

* 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 <u>not</u> 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

Pediatrics 1981;67;217

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 1. Results of Human Leukocyte Antigen Typing on Circulating Lymphocytes*

Individual Tested	HLA Antigens
Patient pre-GVHD	Not performed
Patient's mother	A2, AW24, B40, BW50
Patient's father	Deceased
Blood donor 1	A1, AW24, B8, BW44
Blood donor 2	A3, X, B7, BW35
Patient during GVHD	A3, X, B7, BW35

* Abbreviations used are: HLA, human leukocyte antigen; GVHD, graft versus host disease.

From the [1]Department of Medical Oncology, the [2]Department of Internal Medicine, and the [3]Department of Dermatology, Ankara University School of Medicine, Ibni Sina Hospital, Ankara, Turkey

Post-Transfusion Acute Graft Versus Host Disease in a 17-Year-Old Girl with a Malignant Mesenchymal Tumor – Report of a Case

G. Utkan[1], A. Buyukcelik[1], O. Demir[2], H. Sanli[3] and *A. Pamir[1]*

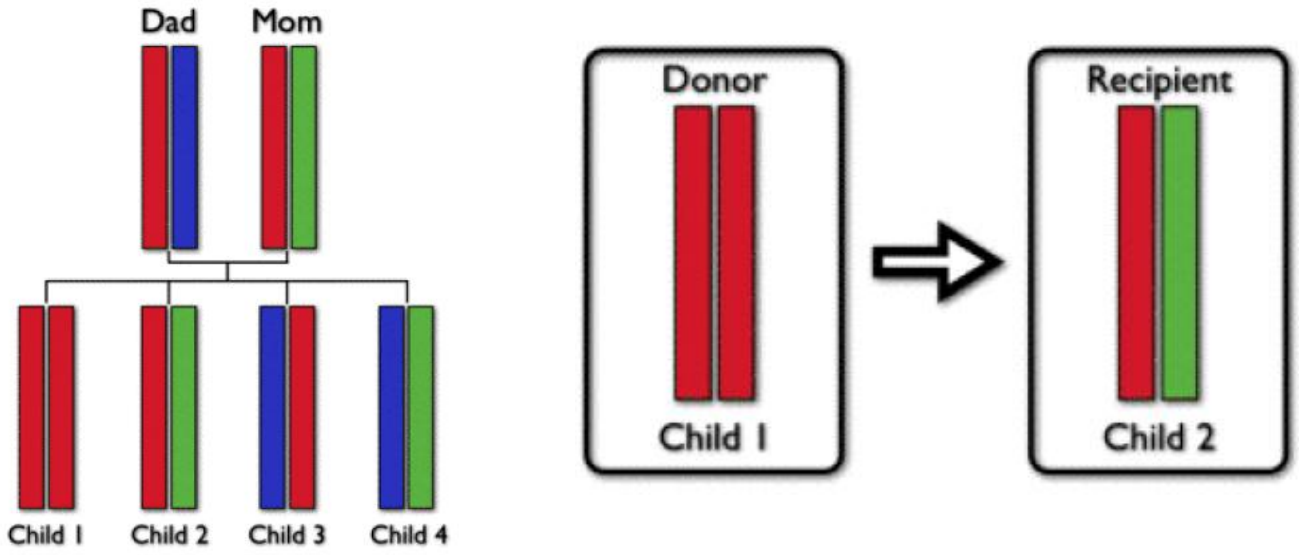
- A 17-year-old girl diagnosed as having alveolar rhabdomyosarcoma in the right crus that was metastasized to the left breast
  - began to be treated with VAC (vincristine, actinomycin D and cyclophosphamide) ->(vincristine, doxorubicin and cyclophosphamide) -> high dose ifosfomide
  - Radiation to Thymus ?
    - 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 1. Patient and implicated blood donor HLA type

Patient	*A* 1,2	*B* 8,44	*C* 7, 5/8	*BW* 6,4	*DRB1* 15,17	*DRB3* 51,52	*DQB1* 6,2
Donor	*A* 1	*B* 8	*C* 7	*BW* 6	*DRB1* 17	*DRB3* 52	*DQB1* 2



Back to Clinical Case

- Chemotherapy Agents: BEP
  - Bleomycin: Glycopeptide
  - Etoposide: Topoisomerase inhibitor
  - Platinum: Cross link DNA → 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-I), 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 immunosupressive drugs and biological agents are introduced into practice, there is a need for regular review of recommendations regarding irradiated blood components.