Centre universitaire de santé McGill
McGill University Health Centre

Technology Assessment Unit of the McGill University Health Centre (MUHC)

Brief report

X-ray versus gamma irradiation of blood components for prevention of transfusion-associated graft versus host disease

Report number:51

DATE: April 12, 2011

Report available from http://www.mcgill.ca/tau

Brief Report prepared for the Technology Assessment Unit (TAU)

of the McGill University Health Centre (MUHC)

by

Alison Sinclair

Brief reports *are prepared in response to urgent requests for information. They contain no recommendations. They are reviewed by the Director and the Chair, but are not submitted to the Executive Committee.*

ACKNOWLEDGEMENTS

With thanks to the following individuals for responding to questions and requests for information:

- Ginette Lebel, Assistant Head, Transfusion Services, Montréal Children's Hospital
- Ann Wilson, Transfusion Services, Montréal Children's Hospital
- Linh-Chi Nguyen, Department of Biomedical Engineering, McGill University Health Centre

We are grateful to Dr M Warner, Head, Division of Haematology, MUHC, and Dr. Christian Janicki, Radiation Safety Manager, Radiation Protection Service (Quality Management), MUHC for reviewing a draft of this report**.**

TABLE OF CONTENTS

LIST OF TABLES

SUMMARY

Background: Irradiation of blood components for the prevention of transfusion-associated graft versus host disease (TA-GvHD) in immunosuppressed or otherwise at-risk patients is a long-established practice. The Montréal Children's Hospital is investigating replacement of its 29-year-old Caesium-137 source (gamma) irradiator with either an updated model of a gamma irradiator or an X-ray irradiator (Gammacell 1000GE Elite, or Raycell CE, both made by Best Theratronics).

Objective: The Technology Assessment Unit (TAU) was asked to review the available evidence in order to determine whether the two technologies were comparable in terms of effectiveness. (Comparison of costs has been carried out by the Biomedical Engineering Department.)

Findings: The majority of blood irradiators in operation are gamma-ray irradiators, with X-ray irradiators having been relatively recently brought on the market. Most evidence on the effectiveness of irradiation has been collected on blood irradiated with gamma rays. A direct, randomized comparison of X-ray irradiation versus gamma irradiation is likely not feasible given the rarity of TA-GvHD.

The cellular response to a given dose of ionizing radiation is the same, regardless of source. There is experimental evidence that X-rays and gamma rays have equivalent effectiveness in ablating the proliferative potential of the lymphocytes responsible for TA-GvHD. That evidence has been sufficient for the UK Transfusion Services to issue a 2009 Change Notification indicating that X-rays and gamma rays can be considered equivalent. The British Committee for Standards in Haematology recommends the use of X-rays as an alternative to gamma rays in a 2011 guideline. The American Association of Blood Banks Standards allows for alternative methods of irradiation to gamma rays that are equivalent and have been cleared by the FDA.

Conclusions:

- No studies have been identified that directly compare the effectiveness of X-ray and gamma irradiation for the purpose of irradiating blood to eliminate TA-GvHD.
- On the basis of an understanding of the mechanism of disease and considerable data on cell response to ionizing radiation, it is expected that X-rays and gamma rays would have equivalent effectiveness in ablating the proliferative potential of cells responsible for TA-GvHD.
- The Joint Professional Advisory Committee of the UK Transfusion Services on blood components has recommended X-ray irradiation as a suitable, safe alternative that is equivalent to gamma ray irradiation.
- The capacity of both machines being investigated by the MUHC should be sufficient to meet the annual demand.

LIST OF ABBREVIATIONS

AABB	American Association of Blood Banks
Co-60	Cobalt-60
Cs-137	Caesium-137
Gy	Gray(s), absorbed dose of ionizing radiation, absorption of one joule of ionizing radiation by one kilogram of matter
HLA	human leukocyte antigen
MCH	Montréal Children's Hospital
MUHC	McGill University Health Centre
TA-GvHD	transfusion-associated graft versus host disease
TAU	Technology Assessment Unit

X-ray versus gamma irradiation for prevention of transfusion-associated graft versus host disease

1. BACKGROUND

Irradiation of blood components prior to transfusion in immunocompromised patients is a routinely used precaution to prevent transfusion-associated graft-versus-host disease (TA-GvHD). This disease is a rare complication of blood transfusion, but is fatal in >80% of cases[1-3]. TA-GvHD results from the engraftment of replication-competent donor lymphocytes which then mount an immune response against host tissues, notably bone marrow[4, 5]. This leads to profound bone marrow aplasia, pancytopenia, and, in most cases, death from infection within a month of the transfusion.

The Montreal Children's Hospital is considering replacement of its 29-year old blood irradiator, which uses gamma rays from a Caesium-137 (Cs-137) source to irradiate blood components for transfusion. The options are to purchase an updated gamma irradiator, or to replace it with an X-ray irradiator, which does not pose the security risks or entail the additional regulatory compliance associated with a radioactive source[6]. The Technology Assessment Unit was asked to compare the efficacy and effectiveness of X-ray irradiation versus gamma irradiation.

The Biomedical Engineering Department of the MUHC has already compiled a detailed comparison of the costs of purchase and maintenance of the current models of gamma- and X-ray irradiators, the Gammacell 1000GE Elite and Raycell CE, respectively (both from Best Technologies). Discussion of the security needs and regulatory compliance requirements associated with use of a Cs-137 irradiator is beyond the scope of this document.

Risk of TA-GvHD

TA-GvHD was first reported in transfusion recipients with immunodeficiency[4, 5, 7, 8]: premature infants and children with inherited immunodeficiencies, patients with hematological malignancies, and patients with other malignancies receiving immunotoxic therapy. It has not so far been described in patients with HIV/AIDS[5, 7, 8]. Subsequently, immunocompetent recipients were found to be at risk if they and the donor shared an HLA allotype, either by being blood relatives, or by chance[4]. Risk of TA-GvHD from inadvertent matching of HLA allotype in an unrelated donor varies across populations[9], with higher incidence in relatively homogenous populations, eg, Japan[9, 10]. The overall incidence of TA-GvHD in at-risk adults was estimated as 0.1-1% in the mid-1980s[11], but few other estimates have been produced. Reviewing risks of transfusion in Canada, Kleinman[12] estimated the risk of TA-GvHD in immuno-incompetent recipients as being close to zero, given current practice, and

the risk in unrelated donor transfusions in Canada as 1 in 2 983 to 21 157. Based on the number of cases reported to hemovigilance and in the literature, he estimates the overall risk as less than 1 per million. He suggests that in practice, storage of blood prior to transfusion, which is usual, decreases lymphocyte viability and risk of TA-GvHD[12]. Cases may also be unrecognized or unreported.

No effective therapy has been identified for TA-GvHD[5], and therefore practice centres on prevention through irradiation of blood products prior to transfusion of patients who are considered at risk of TA-GvHD, either those who are known to be at risk due to immunodeficiency, or who will be receiving blood from a related donor[2, 5, 13-15]. With the exception of Japan[13], blood given to an unrelated, immunocompetent recipient is not irradiated.

2. OBJECTIVES

The Technology Assessment Unit (TAU) was asked by Danielle Lamy, Associate Director, Quality and Risk Management, MUHC.

- To establish whether irradiation of blood products using an X-ray source was of equivalent effectiveness to irradiation using gamma rays from a Cs-137 source (Comparison of costs has been carried out by the Biomedical Engineering Department).
- To determine whether the Gammacell and Raycell machines under consideration would meet the annual demand at the MUHC.

3. METHODS

Ovid/Embase and PubMed were searched using the terms: transfusion-associated graft versus host disease (mapped to keywords, and searched as text variations); TA-GvHD; blood transfusion, limited to adverse effects, and irradiation; blood transfusion and graft versus host disease; gammacell, and raycell. The Cochrane database, DARE database, and INAHTA databases were searched for text variations of the above terms. Only scientific articles or documents published in English or French were retained. Reviews and guidelines retrieved were hand searched.

4. LITERATURE REVIEW: EFFECTIVENESS

There are no reports of randomized or nonrandomized comparison of the effect of irradiation by X-rays versus gamma rays on the incidence of TA-GvHD; nor is such a direct comparison likely to be feasible, given the rarity of the outcome. Only one

guideline, from the British Committee for Standards in Haematology Blood transfusion task force[2], makes explicit reference to the use of X-ray irradiation as an alternative to gamma irradiation[16]. Other major national guidelines, eg, from the US and Japan, presently only include recommendations for gamma ray irradiation[13, 14], although the America Association for Blood Banks Standards allows for alternative methods of irradiation that are demonstrated to be equivalent and cleared by the FDA[14]. Guidelines published in languages other than English or French, or that concerned individual institutions or subspecialties, were not reviewed.

Current transfusion guidelines in several countries recommend doses of 20-35 Gy to the centre of the component, to eliminate the proliferative capacity of lymphocytes, with an upper limit of 50 Gy to avoid damaging other cell components[1, 2, 13-15]. No safety concern has been identified for irradiated blood components, although irradiation reduces shelf-life due to increased leakage of intracellular potassium[5, 17]. The evidence on which these guidelines and practice are based were primarily obtained using gamma irradiation with a Cs-137 or Cobalt-60 (Co-60) source[5, 18, 19], although X-ray sources have been mentioned as being used for irradiation of blood products in the past.

A recent review found no reports that evaluated the biological effectiveness of X-rays vs ^{137}Cs gamma rays[6]. However, there is no physical difference between gamma- and X-rays[6], and cellular response to a given dose of ionizing radiation is reported to be the same, regardless of source[20]. One published *in vitro* study has compared red cell membrane permeability and lymphocyte proliferation between blood irradiated with Cs-137 and X-rays and found clinically insignificant differences in permeability, and no difference in lymphocyte function (although this is based on a single experiment)[1]. On the basis of this and other (unpublished) studies[21] reviewed by the Standing Advisory Committee on Blood Components of the UK Transfusion Services, a Change Notification was issued in 2009 to the Guidelines for the Blood Transfusion Services in the United Kingdom (7th Edition, 2005)[15], which stated that "gamma- and X-irradiation can be regarded as equivalent"[16]. Subsequently, blood X-ray irradiation was recommended as a suitable, safe alternative to gamma ray irradiation in a 2011 UK guideline by the British Committee for Standards in Haematology blood transfusion task force[2]. The American Association for Blood Banks Standards allows for alternative methods of irradiation that are demonstrated to be equivalent and cleared by the FDA[14]. The Raycell was cleared by the FDA in 2003[22], and its predecessor the RS 3000 in 1997[23].

5. ANNUAL DEMAND AT THE MUHC

The MCH owns and operates a single Gammacell 1000, capable of irradiating a single unit of blood component at a time, and currently requiring 12 minutes of irradiation time owing to the aging of the Cs-137 source. That unit is used for urgent

or emergency irradiation of blood components for pediatric transfusions, while irradiated blood components for non-urgent pediatric and all adult transfusion are supplied by HemaQuebec. Estimated current urgent/emergency demand is 1148 units of blood components (estimates supplied by Ginette Labelle) annually, equivalent to an estimated 230 hours of operation (not including set-up or transport), or 28.7 8-hour days, at 12 minutes per unit.

Both irradiators under consideration can accomodate up to 4 units simultaneously, although it is likely that single runs will be needed to respond to emergency requests. Projected irradiation times are 7.1 minutes and 4.2 minutes for the Gammacell 1000 Elite and Raycell CE respectively. Assuming 7-minute single runs, the total running time for the current 1148 units would be reduced to 133 hours, or 16 8-hour days. Over time, irradiation times for the Gammacell irradiator would increase with the decay of the Cs-137 source (half-life ~30 years), while the Raycell irradiation times would remain unchanged.

6. DISCUSSION

Irradiation of blood components with gamma rays and occasionally with X-rays[24] for the prevention of TA-GvHD is a long-established practice. There is less clinical experience with X-ray irradiation than gamma-ray irradiation, and the current models of X-ray irradiators have been in use for a relatively short time[25]. The first US sale of a Raycell was in 2004[26] (although the previous unit, the RS 3000, was on the market from 1998), and there are no units installed in Canada (Linh-Chi Nguyen, personal communication).

The practice of irradiation of blood was established based on the understanding of the mechanism of the disease derived from in vitro and animal experiments, the known effect of irradiation on blood components, clinical experience of bone marrow transplant (where the use of irradiated cell components in supportive transfusion was established early to reduce the risk of GvHD[27]), and the clinical observation that TA-GvHD has almost ceased to be reported in patients receiving appropriately irradiated blood[3] (see Table 1).

The responses of T-lymphocytes and other cellular blood components to irradiation *in vitro* have been extensively characterized[17, 19, 28]. X-ray irradiation can deliver the required level and uniformity of exposure to ablate the proliferative potential of lymphocytes[1, 2, 24], although one reviewer notes that the relative effects have yet to be characterized fully[6].

7. CONCLUSIONS

- No studies have been identified that directly compare the effectiveness of X-ray and gamma irradiation for the purpose of irradiating blood to eliminate TA-GvHD.
- On the basis of an understanding of the mechanism of disease and considerable data on cell response to ionizing radiation, it is expected that X-rays and gamma rays would have equivalent effectiveness in ablating the proliferative potential of cells responsible for TA-GvHD.
- The Joint Professional Advisory Committee of the UK Transfusion Services on blood components has recommended X-ray irradiation as a suitable, safe alternative that is equivalent to gamma ray irradiation.
- The capacity of both machines being investigated by the MUHC should be sufficient to meet the annual demand.

TABLE

Table 1 Reported cases of TA-GvHD

Reference	Reports of cases
Brubaker, 1983[11]	incidence in immuno-compromised adults 0.1-1%.
Rappeport, 1990[7]	incidence "unknown and probably higher than the 60-70 cases reported in the literature"
Andersen, 1991[29]	Survey of AABB members, 44 reported cases to 1989
Greenbaum, 1991[3]	131 cases found on literature review to October 1990; 113 received non-irradiated blood from healthy donors; 17 received non-irradiated WBCs from donors with CML; 1 received multiple irradiated (20 Gy) blood components.
Kleinman, 2003[12]	4 recent cases (2 reported to Health Canada since 1992, 2 presented at meeting in 2000, both patients received non-irradiated blood). None reported to Quebec hemovigilance in 2000
Sazasma, 1994[4]	51 cases published before 1988 in English, 65 cases published since
Williamson, 2009[30]	SHOT database, UK. 12 cases 1996-1999, 1 2000-2003; 11 without leukodepletion, 2 with[†].
Juji, 2009[31]	Japanese experience. 1981-1986, retrospective analysis TA-GvHD following cardiovascular surgery gave risk of 1:659 cases; 1993-1997, 14 cases reported to hemovigilance; 2000, started irradiation of all cellular blood components; 2000 on, no cases TA-GvHD
Momose, 2009[32]	No confirmed cases in Japan, 2004-2008; one suspected, with non-irradiated blood from related donors

AABB, American Association of Blood Banks; CML, chronic myelogenous leukemia; SHOT, Serious Hazards of Transfusion; WBC, white blood cells

[†]Involves physical removal of white cells by filtering. Since there have been reports of TA-GvHD following receipt of blood that was leukodepleted only, it is not presently regarded as sufficient prevention in itself.

REFERENCES

1. Janatpour K, Denning L, Nelson K, Betlach B, Mackenzie M, Holland P. Comparison of X-ray vs. gamma irradiation of CPDA-1 red cells. Vox Sang 2005;89(4):215-219.

2. Treleaven J, Gennery A, Marsh J et al. Guidelines on the use of irradiated blood components prepared by the British Committee for Standards in Haematology blood transfusion task force. Br J Haematol 2011;152(1):35-51.

3. Greenbaum BH. Transfusion-associated graft-versus-host disease: historical perspectives, incidence, and current use of irradiated blood products. J Clin Oncol 1991;9(10):1889-1902.

4. Sazama K, Holland PV. Transfusion-induced graft-versus-host-disease. In: Garraty G, editor. Immunobiology of Transfusion Medicine. New York, NY: M. Decker; 1994.

5. Dwyre DM, Holland PV. Transfusion-associated graft-versus-host disease. Vox Sang 2008;95(2):85-93.

6. Dodd B, Vetter RJ. Replacement of 137Cs irradiators with x-ray irradiators. Health Phys 2009;96(2 Suppl):S27-S30.

7. Rappeport JM. Transfusion-associated graft-versus-host disease. Yale J Biol Med 1990;63(5):445-454.

8. Rühl H, Bein G, Sachs UJH. Transfusion-associated graft-versus-host disease. Transfus Med Rev 2009;23(1):62-71.

9. Wagner FF, Flegel WA. Transfusion-associated graft-versus-host disease: risk due to homozygous HLA haplotypes. Transfusion 1995;35(4):284-291.

10. Ohto H, Anderson KC. Survey of transfusion-associated graft-versus-host disease in immunocompetent recipients. Transfus Med Rev 1996;10(1):31-43.

11. Brubaker DB. Human posttransfusion graft-versus-host disease. Vox Sang 1983;45(6):401-420.

12. Kleinman S, Chan P, Robillard P. Risks associated with transfusion of cellular blood components in Canada. Transfus Med Rev 2003;17(2):120-162.

13. Asai T, Inaba S, Ohto H et al. Guidelines for irradiation of blood and blood components to prevent post-transfusion graft-vs.-host disease in Japan. Transfus Med 2000;10(4):315-320.

14. American Association of Blood Banks. AABB Guidelines and Standards for Blood Banks and Transfusion Services. 23 ed. Basel, Switzerland: Karger; 2007.

15. The Stationary Office. Guidelines for the Blood Transfusion Services in the UK. 7 ed. London: The Stationary Office; 2005.

16. McLellan S. X-irradiation as an alternative to -irradiation. Change Notification UK National Blood Services No. 6 - 2009. http://www transfusionguidelines org/docs/pdfs/dl_change_note_2009_06 pdf, 2009. Accessed March 22, 2011. Available from http://www.transfusionguidelines.org/docs/pdfs/dl_change_note_2009_06.pdf.

17. Weinmann M, Hoffmann W, Rodegerdts E, Bamberg M. Biological effects of ionizing radiation on human blood compounds ex vivo. J Cancer Res Clin Oncol 2000;126(10):584-588.

18. Leitman SF. Use of blood cell irradiation in the prevention of posttransfusion graft-vs-host disease. Transfusion Science 1989;10(3):219-232.

19. Pelszynski MM, Moroff G, Luban NL, Taylor BJ, Quinones RR. Effect of gamma irradiation of red blood cell units on T-cell inactivation as assessed by limiting dilution analysis: implications for preventing transfusion-associated graft-versus-host disease. Blood 1994;83(6):1683-1689.

20. Hall EJ, Giaccia AJ. Radiobiology for the radiologist. Philadelphia : Lippincott Williams & Wilkins, 2006.

21. Thomas S, Cardigan R. X-ray irradiation of blood components. http://www transfusionguidelines org uk/docs/pdfs/dl_support_jpac-08-75 pdf, 2008. Accessed March 22, 2011.

22. FDA US Food and Drug Administration. Device approvals and clearances. 510(k) clearances. September 2003. http://www fda gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm091159 htm, 2003. Available from http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm091159.ht.

23. FDA US Food and Drug Administration. 50(k) Clearance, RS3000 Shielded Cabinet X-ray Radiation Source (Blood Irradiator). http://www accessdata fda gov/cdrh_docs/pdf/K974210 pdf, 1997. Available from http://www.accessdata.fda.gov/cdrh_docs/pdf/K974210.pdf.

24. Moroff G, Leitman SF, Luban NL. Principles of blood irradiation, dose validation, and quality control. Transfusion 1997;37(10):1084-1092.

25. Tadokoro K, Reesink HW, Panzer S et al. Problems with irradiators. Vox Sang 2010;98(1):78-84.

26. News Medical. First North American sales of Raycell X-ray blood irradiator. http://www news-medical net/news/2004/03/30/209 aspx, 2004. Accessed March 22, 2011. Available from http://www.news-medical.net/news/2004/03/30/209.asp.

27. Thomas E, Storb R, Clift RA et al. Bone-marrow transplantation (first of two parts). N Engl J Med 1975;292(16):832-843.

28. Button LN, DeWolf WC, Newburger PE, Jacobson MS, Kevy SV. The effects of irradiation on blood components. Transfusion 1981;21(4):419-426.

29. Anderson KC, Goodnough LT, Sayers M et al. Variation in blood component irradiation practice: implications for prevention of transfusion-associated graft-versus-host disease. Blood 1991;77(10):2096-2102.

30. Williamson LM, Stainsby D, Jones H et al. The impact of universal leukodepletion of the blood supply on hemovigilance reports of posttransfusion purpura and transfusion-associated graft-versus-host disease. Transfusion 2007;47(8):1455-1467.

31. Juji T, Watanabe Y, Uchida S et al. How we Could overcome transfusion associated graft-versus-host disease (TA-GVHD) in Japan. Vox Sang 2009;97:9.

32. Momose S, Taira R, Muraoka M et al. Haemovigilance data for five years by Japanese Red Cross Blood Service: Transfusion-related adverse reactions and infections from 2004 to 2008. Vox Sang 2009;97:165.