Efficacy of HLA-matched platelet transfusions for patients with hypoproliferative thrombocytopenia: a systematic review

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BACKGROUND: HLA-matched platelets (PLTs) are widely used to transfuse patients but the effectiveness of HLA matching has not been well defined and the cost is approximately five times the cost of preparing the random-donor PLTs. The objective of this systematic review was to determine whether HLA-matched PLTs lead to a reduction in mortality; reduction in frequency or severity of hemorrhage; reduction in HLA alloimmunization, refractoriness, or PLT utilization; or improvement in PLT count increment in patients with hypoproliferative thrombocytopenia.

STUDY DESIGN AND METHODS: We conducted a literature search of MEDLINE, Cochrane Controlled Register of Clinical Trials, EMBASE, and PubMed databases to April 2012.

RESULTS: A total of 788 citations were reviewed and 30 reports were included in the analysis. Most studies did not include technologies currently in use for HLA typing or detection of HLA antibodies as 75% were conducted before the year 2000. None of the studies were adequately powered to detect an effect on mortality or hemorrhage. HLA-matched PLTs did not reduce alloimmunization and refractoriness rates beyond that offered by leukoreduction, and utilization was not consistently improved. HLA-matched PLTs led to better 1-hour posttransfusion count increments and percentage of PLT recovery in refractory patients; however, the effect at 24 hours was inconsistent.

CONCLUSION: The correlation of the PLT increment with other clinical outcomes and the effect of leukoreduction on HLA-matched PLT transfusion could not be determined. Prospective studies utilizing current technology and examining clinical outcomes are necessary to demonstrate the effectiveness of HLA-matched PLT transfusion.

Platelet (PLT) refractoriness refers to persistent suboptimal PLT count increment after a PLT transfusion. In the 1960s PLT refractoriness was identified as a major complication of chronic PLT transfusions and linked to complement-fixing isoantibodies.[1,2] In 1969, Yankee and colleagues postulated that the likely target for these antibodies was the newly described HLA antigen;[3] they transfused PLTs from HLA-identical siblings to patients refractory to random-donor PLTs and found better posttransfusion count increments.[3]

ABBREVIATIONS: CREG(s) = cross-reactive group(s); RCT = randomized controlled trial; TMM(s) = triplet amino acid mismatch(-es).

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Yankee and colleagues[4] then demonstrated that PLTs from HLA-matched unrelated donors had the same effect. HLA-matched PLT transfusion has become a standard of care for patients with PLT refractoriness in many centers as refractoriness has been linked to inferior clinical outcomes, including bleeding and mortality[5,6] as well as higher health care costs.[7]

Alloimmunization to PLT antigens, however, accounts for only approximately 20% of cases of refractoriness,[8] and results from exposure to contaminating white blood cells in PLT products.[9] A number of controlled trials, particularly the Trial to Reduce Alloimmunization to Platelets (TRAP), have shown that leukoreduction leads to significantly decreased rates of alloimmunization and refractoriness.[10] In Canada after implementation of universal prestorage leukoreduction the rates of alloimmunization have decreased from 19% to 7%, refractoriness from 14% to 4%, and proportion of patients requiring HLA-matched PLTs from 14% to 5%.[11]

There are a number of methods used to select HLA-matched PLT products for refractory patients. Commonly, recipient and donor are matched for HLA A and B antigens as the most commonly involved antibodies are directed against HLA Class I A and B antigens.[3] The grading of the quality of matches is as follows: A (donor and recipient match at four of four antigens), B (all donor antigens are present in the recipient phenotype but the donor lacks one [B-1] or two [B-2] of the recipient antigens), and C (donor possesses one or more antigens not found in the recipient).[12] Duquesnoy and colleagues[13] revised the grading criteria to include "permissive" mismatches. HLA A and B antigens can be organized into cross-reactive groups (CREGs) on the basis of which public epitopes they share. The majority of HLA antibodies have been shown to be directed against public epitopes[14] so that precise HLA matching was not necessary. PLTs with one or two mismatches could be used as long as these antigens fell within the same CREG.[15] Another method, the antibody specificity prediction method, identifies the specificity of HLA antibody and antigen negative PLT products are provided based on the antibody specificity.[16] Recently, the software tool HLAMatchmaker has been used to predict HLA compatibility by identifying immunogenic epitopes represented by amino acid triplets (eplets) in antibody-accessible regions of HLA molecules.[17]

Regardless of the method, provision of HLA-matched PLTs is a costly and time- and labor-intensive process. The cost per procedure of PLT concentrate preparation by HLA matching is approximately five times that of the random-donor concentrate.[18] From the literature, it is not clear which of the available HLA-matching methods is most cost-effective and, more importantly, the most likely to result in improvement in patients' clinical outcomes. We conducted a systematic review to determine whether HLA-matched PLT transfusions administered to patients with hypoproliferative thrombocytopenia improved clinical outcomes to guide development of a guideline on PLT transfusion.

MATERIALS AND METHODS

Information sources and search

The search strategy was developed by one of the authors (KP) and an information specialist. The search was applied to electronic databases MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and PubMed from 1948 to March 2011 using the following medical subject headings and text words: "blood transfusion," "blood platelets," "blood component transfusion," "platelet transfusion," "HLA antigens," "histocompatibility antigens," "human platelets antigens," "HLA antigen," "HL-A antigen," "HPA antigen," "thrombocytopenia," "blood group incompatibility," "alloimmunity," "alloimmunization," "refractory," "refractoriness," and "neonatal alloimmune thrombocytopenia." The search was updated to April 2012. The full search strategy is shown in Appendix S1 (available as supporting information in the online version of this paper).

Study selection

Two reviewers (KP, NS) independently assessed the citations to identify studies that met all the following inclusion criteria: 1) an original article, 2) included 10 or more patients with hypoproliferative thrombocytopenia, and 3) included any of the outcomes of interest: the primary outcomes of mortality and hemorrhage and the secondary outcomes of PLT refractoriness, alloimmunization, utilization, and the PLT increment. A study was excluded if it was an editorial, letter, or review. We did not include studies that used cross-matching to select compatible PLT products.

If there was disagreement, the full report was retrieved and independent assessment was repeated. Disagreements for inclusion were resolved by consensus.

Data collection process and data items

Three reviewers (KP, NS, ST) independently extracted data from the included reports to the tables. Data extracted from each of the studies included 1) study characteristics (year of publication, country site, study site whether single or multicentered, patient population, treatment, and sample size); 2) types of outcome (mortality and hemorrhage or bleeding, PLT refractoriness or alloimmunization, PLT utilization, and the PLT increments); and 3) quality of individual studies.

Assessing the quality of individual studies

The assessment of the quality of randomized control trials and nonrandomized studies was based on the Cochrane

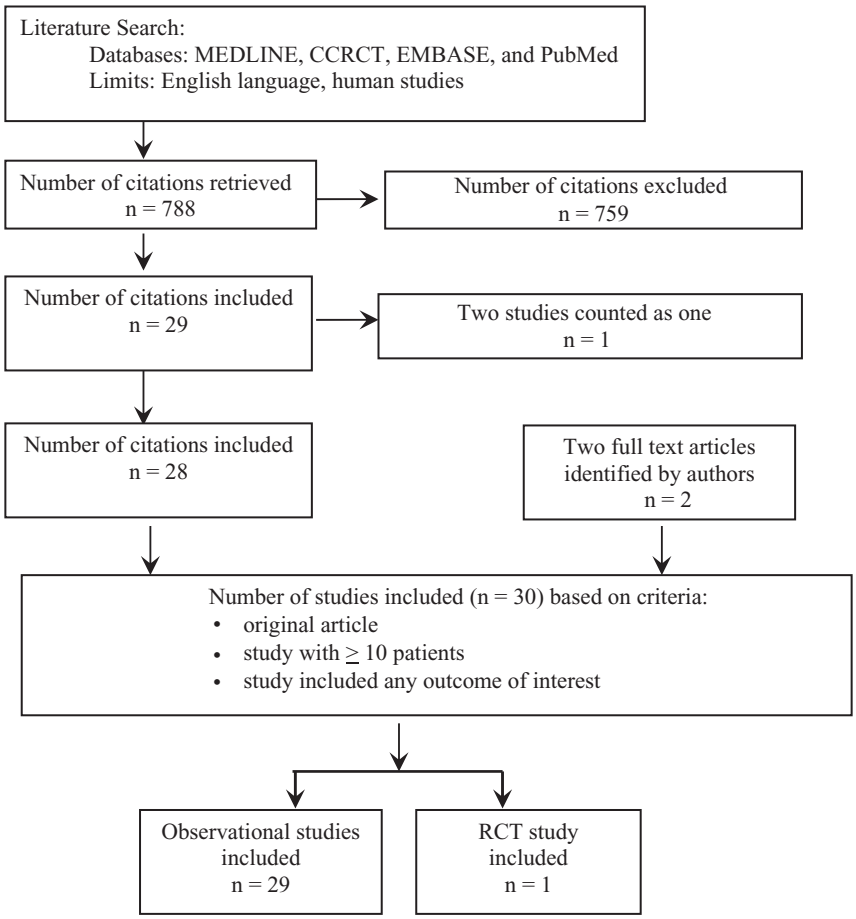

Fig. 1. Flow diagram of the study selection process.

Collaboration's tool in assessing risk of bias[19] and a checklist developed by Fowkes and Fulton,[20] respectively.

Method of analysis

A meta-analysis was not conducted due to considerable heterogeneity in the measurement of study outcomes. Subgroup analysis was performed based on whether patients were refractory or nonrefractory and whether PLT products were leukoreduced.

RESULTS

Study selection

A total of 788 citations were retrieved. Of these, 759 were excluded because they did not fulfill eligibility criteria: 320 were not original studies of patients with hypoproliferative thrombocytopenia, 327 did not include 10 or more patients with hypoproliferative thrombocytopenia, and 112 did not include at least one of the outcomes of interest. The full reports of the remaining 29 citations that met the inclusion criteria were retrieved. Two studies reported different outcomes on the same population and were counted as one.[13,21] Two additional articles were later identified by authors bringing the total to 30 studies.

One randomized controlled trial (RCT) and 29 nonrandomized studies were included in this review. One study, although described in the tables, did not contribute to this report as it was a study with a retrospective and prospective component and there was no analysis of the retrospective study and the prospective component only included nine patients.[22] The observational studies consisted of 15 prospective and 14 retrospective studies. The flow diagram for study inclusion is shown in Fig. 1. Patients were provided HLA-matched PLTs based on antigen matches or HLA antibody specificities identified using various techniques or by using a software algorithm to determine HLA compatibility that identifies immunogenic epitopes on HLA molecules.[17]

Characteristics and quality of studies

RCT

The single-center study randomized 78 patients with nonrefractory hypoproliferative thrombocytopenia of whom 33 received PLT transfusion and were analyzed (Tables 1 and 2; Table S1, available as supporting information in the online version of this paper).[23] Patients received nonleukoreduced irradiated products. The assessment of bleeding was not standardized a priori and the sample size was not predetermined to assess differences in bleeding outcomes.

Nonrandomized studies

Table S2 (available as supporting information in the online version of this paper) describes the characteristics of the nonrandomized studies. Seventy-five percent were published before the year 2000 and 62% before 1990. Twenty-one of the 29 nonrandomized studies were conducted in the United States, two in the Netherlands and one each in Italy, United Kingdom, Canada, Australia, Taiwan, and New Zealand. Twenty-six were single centered,[12,13,16,17,22,24-44] and three were multicentered.[45-47] The 29 studies enrolled 1671 patients and sample sizes ranged from 11[12] to 208 patients.[16] The patient population was largely an adult population as only two studies enrolled only pediatric patients.[24,26] Fifteen studies were prospective[13,16,24-34,45,46] and 14 were retrospective.[12,17,22,35-44,47]

Twenty-one of the nonrandomized studies focused on patients with refractory thrombocytopenia,[12,13,16,17,22,27,29,30,32-35,37-42,44,45,47] and the definitions of

TABLE 1. Characteristics and outcomes of the RCT

First author, year	Country	Center status	Population	Treatment	Sample size	Mortality	Hemorrhage	Refractoriness/HLA alloimmunization	PLT utilization	PLT count increment	Duration of follow-up
Messerschmidt, 1988[23]	United States	Single	Newly diagnosed HT for experimental therapies (age, 2-52 years)	HLA matched vs. mismatched, IR, SDP	15 18	NR	3 bleeding episodes vs. 9 (p = ns)	2/0 5/5 (p value NR)	Median 3 vs. 5 (p = 0.08)	No difference	NR

HT = hypoproliferative thrombocytopenia; IR = irradiated; NR = not reported; ns = not significant; SDP = single-donor PLTs.

TABLE 2. Quality of the RCT

First author, year	Adequate sequence generation, yes or no	Allocation adequately concealed, yes or no	Blinding method, yes or no	Adequate blinding, yes or no	Intention-to-treat analysis, yes or no	Outcome data complete, yes or no	Incomplete data assessed, yes or no	Selective reporting of outcomes, yes or no	Adequate follow-up, yes or no	Proportion lost to follow-up, yes or no
Messerschmidt, 1988[23]	NR	Yes	Yes	No	No	Yes	NR	No	NR*	NR

* "Patients were continued on the trial until bleeding from thrombocytopenia necessitated more than two platelet transfusions (greater than eight units) within 24 hours, or chemotherapy ended," but the number who were analyzed were not included to allow for appropriate assessment of adequate follow-up.
NR = not reported.

refractoriness were variable (Table S2). Ten transfused leukoreduced PLTs[16,21,24,25,27,28,30,33,34,36] (Table 3), of which five used prestorage leukoreduced PLTs,[21,24,30,33,34] three used poststorage leukoreduction,[16,25,27] and two did not specify whether leukoreduction was conducted pre- or poststorage.[25,28] Nineteen studies indicated single-donor PLTs were used.[12,13,16,24,26-28,30-34,37,38,40,41,43-45]

The assessment of study quality is displayed in Table S3 (available as supporting information in the online version of this paper). Nine of the 29 studies did not specify the source of sample of patients, that is, how patients were recruited.[22,24,25,29,35,36,38,42,43] Eleven studies detailed sampling methods,[12,16,17,26,27,37,38,40,41,46,47] and one indicated that a random sample was selected but a clear definition of randomization was not provided.[25] The sample size was not predetermined in any study and the assessment of the outcomes was not blinded.

Fifteen studies clearly defined the eligibility criteria for inclusion of patients,[13,16,17,26-29,35,37-39,41,45-47] and most provided clear definitions of outcome.[12,13,16,17,22,24-29,31-37,39,41-46] Three studies had acceptable control group and comparable characteristics,[16,28,35] five studies[17,22,29,35,47] described details of quality measures for the collection of data and laboratory tests (e.g., accuracy, reproducibility, calibration), and six analyzed confounding factors that potentially influenced the outcomes.[16,25,27,37,39,46]

Outcomes

RCT

The primary endpoint of the RCT was hemorrhage (Table 1). Although the difference was not significant, patients receiving HLA-matched PLT transfusion had fewer bleeding episodes than patients receiving nonmatched PLTs ($p = 0.095$). Similar results were found for refractoriness (the p value was not stated), alloimmunization (the p value was not stated), and the number of PLT transfusions. There was no difference in PLT increments ($p = 0.20$).

Nonrandomized studies

Our primary outcome, mortality, was described in two studies,[28,44] with only one small study[28] comparing patients who received random donor PLTs that were not leukoreduced to leukoreduced PLTs and leukoreduced PLTs that were HLA matched. There was no difference in mortality (Table 3). In addition, Lohrmann and colleagues[44] reported that six patients died from disease complications and none of the deaths were due to bleeding.

Of the three studies that reported the frequency of hemorrhage as an outcome[24,28,40] only one categorized bleeding according to the World Health Organization's/National Cancer Institute classification system. Grade 3 to 4 hemorrhage occurred in 18% (2/11) of alloimmunized patients who did not receive HLA-matched PLTs[24] whereas none of the 30 alloimmunized patients who received HLA-matched PLTs had Grade 3 to 4 hemorrhage (the p value was not stated). The rate of hemorrhage was not reported for patients who were not alloimmunized and received random-donor PLT transfusion. All PLT products were leukoreduced. Two patients who had refractory thrombocytopenia also developed hemorrhage when receiving non–HLA-matched, nonleukoreduced PLT transfusion.[28] Hemorrhage was not reported in patients who received leukoreduced or HLA-matched and leukoreduced PLT products. However, there was only one refractory patient in the leukoreduced group and no refractory patients in the group that received leukoreduced HLA-matched PLTs.[28] Levy and Woodfield[40] reported that bleeding resolved among patients transfused with HLA-matched PLTs but the frequency of bleeding was not provided (Table 3).

The use of HLA-matched leukoreduced PLTs reduced the rate of refractoriness (0%) and alloimmunization (0%) compared to nonleukoreduced, non–HLA-matched PLTs (23 and 48%, respectively, $p = 0.01$) but did not reduce these rates significantly compared to leukoreduced, non–HLA-matched PLTs (5 and 16%, respectively, p = not significant; Table 3).[28] Although HLA-matched products appeared to reduce PLT transfusion rates, none of the differences were significant (Table 3).[12,28,31]

The PLT count increment was the most commonly reported outcome (Table 4) yet there are only a few trials comparing HLA-matched and unmatched PLT transfusion using leukoreduced HLA-matched PLT products and results were often conflicting.[16,24,34] In the largest comparative study of patients with refractory thrombocytopenia, the response to poststorage leukoreduced HLA-matched PLT transfusion was not higher compared to leukoreduced single-donor PLT transfusion using percentage of PLT recovery as the measure for PLT increment (21 ± 4 vs. 15 ± 1, p = not significant).[16] Smaller studies have shown a difference between HLA-matched and HLA-matched leukoreduced PLTs.[24,34] In pediatric patients with thalassemia undergoing hematopoietic stem cell transplantation, the use of HLA-matched leukoreduced PLTs was associated with a higher increment (43.5×10^8/L) compared to random-donor leukoreduced PLTs (62.5×10^8/L, $p < 0.01$).[24] In the absence of leukoreduction, HLA-matched PLT transfusion has been shown to be associated with a higher PLT increment in comparison to random-donor PLT transfusion[42] (Table 4).

Conflicting results are also evident for comparing cross-matched to HLA-matched PLT transfusion in refractory patients. Heal and colleagues[38] indicated that compatibility by cross-match was the most significant predictor for an increase in the PLT count compared to HLA- and ABO-matched PLTs in agreement with the results of Friedberg and colleagues[27] that showed median corrected count increment (CCI) of at least 7.5×10^9/L for HLA cross-match–compatible PLTs compared to 0 for HLA

TABLE 3. Outcomes of nonrandomized studies

First author, year	Treatment	Sample size	Mortality	Hemorrhage	Refractoriness/HLA alloimmunization	PLT utilization	Duration of follow-up
Prospective							
Marktel, 2010[24]	IR, LR, SDP HLA matched IR, LR non-HLA matched RDP IR LR, RDP	30 alloimmunized 11 alloimmunized 9	NR	Grade 3, 4 bleeding 0/30 2/11 NR p = 0.04	NR	NR	NR
Levin, 2003[25]	RDP, HLA unmatched ABO matched, LR, (IR for PBSCT)	97	NR	NR	NR	NR	NR
Petz, 2000[16]	SDP, LR, HLA vs. SDP, LR, CXM vs. SDP, LR ASP vs. LR, SDP	25 37 35 111	NR	NR	NR	NR	NR
Hogge, 1995[26]	RDP, some SDP, some plasma reduced, some filtered	128	NR	NR	NR	NR	NR
Friedberg, 1994[27]	SDP, RDP if SDP not available, 91% LR	71	NR	NR	NR	NR	NR
Moroff, 1992[45]	HLA-matched SDP	73	NR	NR	NA	NR	NR
Bishop, 1988[46]	HLA unmatched	133	NR	NR	NR	NR	NR
Murphy, 1986[28]	Control: plasma reduced RBCs, SDP vs. LR: filtered RBCs, LR SDP vs. HLA: filtered RBCs, LR SDP matched for 3-4/4 HLA A and B antigens	31 19 11	2 refractory 0 0	NR	7 (23%)/15 (48%) No tx/pregnant (n = 14): 2 (14%)/7 (50%) 1 (5%)/3 (16%) No tx or pregnant (n = 11): 0/1 (9%) p = 0.02 vs. control for HLA alloimmunization 0/0 No tx/pregnant (n = 5): 0/0 p = 0.01 vs. control, p = ns vs. LR for HLA alloimmunization	16 19 9 p = NR	7 weeks
Ware, 1984[29]	HLA matched, RDP	15	NR	NR	NR	NR	NR
Dahlke, 1984[30]	LR, SDP	67	NR	NR	NA	NR	NS
Hester, 1978[31]	SDP	109	NR	NR	NR	HLA 2-antigen match 201 vs. 125 for no HLA antigens matched (p = ns) By 96 hr, 76% of HLA matched required retx vs. 93% of mismatched (p = ns)	NR

TABLE 3. *Continued*

First author, year	Treatment	Sample size	Mortality	Hemorrhage	Refractoriness/HLA alloimmunization	PLT utilization	Duration of follow-up
Macpherson, 1979[32]	SDP HLA matched	12	NR	NR	NR	NR	NR
Duquesnoy, 1977[13,21]	SDP LR	59	NR	NR	NR	NR	NR
Wu, 1977[33]	SDP, LR	21	NR	NR	NR	NR	NR
Herzig, 1975[34]	SDP ± LR	17	NR	NS	NA	NR	NR
Retrospective							
Fontaine, 2011[35]	HLA incompatible by IgG SAB method	13 6 controls with CPRA < 75%	NR	NR	NR	C1q compatible IgG compatible, 29 tx; C1q compatible IgG incompatible, 134 tx; C1q incompatible IgG incompatible, 43 tx	NR
Pai, 2010[22]	NR	Retrospective n = 19 Prospective n = 9	NR	NR	NR	NR	Median 7 months for prospective study
Brooks, 2008[47]	HLAMatchmaker matched PLTs	73	NR	NR	NR	NR	NR
Nambiar, 2006[17]	HLA matched	16	NR	NR	NR	NR	NR
Levin, 2004[36]	HLA matched LR, (IR for PBSCT)	72	NR	NR	NR	NR	NR
McFarland, 1989[37]	SDP	43	NR	NR	NA	NR	NR
Heal, 1987[38]	SDP	51	NR	NR	NA	NR	NR
Klingemann, 1987[39]	RDP	71	NR	NR	NA	NR	NR
Levy, 1984[40]	SDP	14	NR	Bleeding resolved with HLA vs. non-HLA matched PLTs	NR	NR	NR
McElligott, 1982[41]	SDP	21	NR	NR	NA	NR	NR
Daly, 1980[42]	RDP vs. HLA matched	73	NR	NR	NR	NR	NR
Tosato, 1978[12]	HLA-matched SDP	11	NR	NR	NA	NA	40 (up to 46) months
Mittal, 1976[43]	HLA-matched SDP vs. RDP	43	NR	NR	NR	NR	NR
Lohrmann, 1974[44]	SDP	15	6/15 (due to complications of disease)	NR	NA	NR	NR

ASP = HLA antibody specificity prediction method; C1q = first complement component; CXM = cross-match; IgG = immunoglobulin G; IR = irradiated; LR = leukoreduced; NA = not applicable; NR = not reported; ns = not significant; PBSCT = peripheral blood stem cell transplant; RDP = random-donor pooled PLTs; SAB = single antigen beads, SDP = single-donor PLTs; tx = transfusion.

TABLE 4. PLT increments in nonrandomized studies

Author, year	PLT count increment
Prospective	
Marktel, 2010[24]	IR, LR, SDP HLA matched CCI > 4.5 in 74% Median increment: 43.5×10^9/L with HLA matched vs. CCI > 4.5 in 59% Median increment: 36.5×10^9/L for HLA 1 mismatch vs. CCI > 4.5 in 26% and Median increment: 6.25×10^9/L with RDP; $p < 0.01$ for HLA vs. RDP, $p = 0.02$ for random vs. HLA mismatch, $p = 0.16$ for HLA vs. HLA mismatch IR, LR non–HLA-matched RDP CCI > 4.5 in 74% Median increment: 36×10^9/L
Levin, 2003[25]	No correlation between HLA antibodies by ELISA, LCT, LIFT + PIFT, and < 20% 1-hr recovery Positive ELISA and PIFT ($p = 0.04$) and LIFT + PIFT ($p = 0.03$) associated with 16-hr recovery <10%
Petz, 2000[16]	Mean 24-hr PPR: SDP, LR, HLA: 21 ± SEM 4%, p = ns vs. random SDP,LR, CXM: 23 ± SEM 4%, $p = 0.04$ vs. random SDP, LR, ASP: 24 ± SEM 3%, $p = 0.007$ vs. random LR, SDP: 15 ± SEM 1%, $p < 0.01$ for ASP vs. random
Hogge, 1995[26]	11/16 (69%) with LCTABS had 2× CCI with HLA matched PLTs compared to RDP $p < 0.01$, 2/8 (25%) with no LCTABS had response to HLA-matched PLTs p = ns
Friedberg, 1994[27]	SPRCA CXM was better predictor than HLA for 1 hr, Median CCI $\geq 7.5 \times 10^9$/L for HLA CXM compatible vs. 0 for HLA CXM incompatible, $p < 0.007$, Mean CCI for HLA SDP: A + BU 6.1×10^9/L vs. BX + C 3.55×10^9/L vs. SDP, 0, $p < 0$
Moroff, 1992[45]	1-hr CCI $\geq 7.5 \times 10^9$/L, HLA 54% vs. CXM 48%, p = ns, 24-hr CCI $\geq 4.5 \times 10^9$/L, HLA 42%, CXM 23%, $p < 0.05$, 1-hr CCI A, BU 11.0×10^9/L vs. BX 6.0×10^9/L vs. C 9.0×10^9/L vs. D 8.0×10^9/L, p = ns, 1-hr CCI $\geq 7.5 \times 10^9$/L + 24-hr CCI $\geq 4.5 \times 10^9$/L in 53% of HLA-matched CXM compatible vs. 45% with HLA-matched CXM incompatible, p = ns
Bishop, 1988[46]	Mean 1-hr CCI: HLA antibody Grade 0, 15.5×10^9/L vs. Grade 1, 11.6×10^9/L; Grade 2, 8.9×10^9/L; Grade 3, 5.5×10^9/L; Grade 4 mismatch, 5.0×10^9/L
Murphy, 1987[28]	NR
Ware, 1985[29]	1- to 2-hr CCI HLA A match: 6,640 ± 7,290 HLA B match: 7,892 ± 6,857 HLA C match: 8,435 ± 9,820 HLA D match: 5,855 ± 9,027 Random: 18,415 ± 5,386
Dahlke, 1984[30]	CCI from HLA A3 mismatch to A1 or A11 vs. A- and BU-matched PLTs was less, $p < 0.001$, A1 or A11 mismatched to A3 vs. A and BU associated with small increments $p < 0.001$, In B5 group B18, BW16 higher CCI ($p < 0.01$), Lower CCI with B7 and BW21 Low CCI with B5 to B15 and B17 ($p < 0.01$), Low CCI B27 to B7 ($p < 0.01$) and with B8 and B14 bidirectionally and B12 and BW21 bidirectionally ($p < 0.05$)
Hester, 1978[31]	Median 1-hr CCI for afebrile patients with two antigens shared = 12.0×10^9/L vs. 8.0×10^9/L for febrile patients ($p = 0.01$) Median 1-hr CCI for patients with two antigens shared = 12.0×10^9/L vs. $\leq 8.0 \times 10^9$/L in patients with one antigen, no antigen, or unknown ($p < 0.01$) No difference of CCI for one antigen match vs. no antigen match Median CCI related to number of antigens shared and not specific antigen of haplotype
Macpherson, 1979[32]	CCI > 5.0×10^9/L in 40% HLA A match vs. 55% in BX p = ns, vs. 14% in C $p < 0.05$, vs. 21% in D
Duquesnoy, 1977[13,21]	1- and 24-hr recovery 55%-75% and 40% for HLA A and B, HLA C and D recovery less than A and B ($p < 0.001$), 51% responded to HLA C and D PLTs 24-hr % increment by LCT for HLA A2 positive 40% vs. HLA negative 52% with A1, B1U, and B2U, $p = 0.1$, 25% vs. 53%, $p = 0.003$ with B1X, B2UX, B2X, 9% vs. 36% with C, D, $p = 0.0009$
Wu, 1977[33]	1-hr CCI $\geq 10.0 \times 10^9$/L and/or 20 hr $\geq 8.0 \times 10^9$/L in 2/4 (50%) HLA A vs. 0/1 B1 vs. 1/1 (100%) B2 vs. 1/2 (50%) C vs. 10/19 D for related PLTs, 1/1 (100%) HLA C vs. 6/13 HLA D for unrelated
Herzig, 1975[34]	44%-72% of HLA matched tx had 20 hr CCI > 4.5×10^9/L vs. 72%-96% with HLA LR, $p < 0.05$. Median duration of response 3.5 months for RDP vs. >6 months for LR $p < 0.02$, HLA-A and B1 4.5 months vs. B-2 and C 1.5 months $p < 0.01$, duration has not been reached if LR HLA used and no difference between HLA-A and B-1 vs. B-2 and C

TABLE 4. *Continued*

Author, year	PLT count increment
Retrospective	
Fontaine, 2011[35]	Mean 1-hr CCI range: 3.4×10^9 to 28×10^9/L $16.4 \times 10^9$for C1 q compatible, IgG compatible 10.6×10^9, for C1q compatible, IgG incompatible 2.5×10^9, for C1q incompatible, IgG incompatible Number of adequate PLT transfusion: 90% IgG compatible, C1q compatible 62% IgG incompatible, C1q compatible 14% IgG incompatible, C1q incompatible $p < 0.0001$
Pai, 2010[22]	Retrospective study: the 24 CCI and CCI > 4.5/L for CREG, A/BU matched and EBM equivalent and greater than SDP Prospective study: median CCI for A/BU 14.6 (10.5-22.2) vs. CREG, 10.1 (2.1-26.3) vs. EBM 22.03 (9.9-30.9) $p = 0.034$ (for EBM vs. CREG) Successful tx in 85% A/Bu vs. 63% CREG vs. 84% EBM, $p = 0.004$ for EBM vs. CREG
Brooks, 2008[47]	Median 1-hr CCI with TMMs $\leq$ 9 8.0×10^9/L vs. TMMs > 9 6.0×10^9/L ($p < 0.01$) Median 1-hr CCI with EMMs $\leq$ 11 7954×10^6/L vs. EMMs > 11 6356×10^6/L ($p = 0.02$) No difference for 24-hr CCI
Nambiar, 2006[17]	Median 15-min to 1-hr CCI for TMMs $\leq$ 9, 13.5 vs. TMMs> 9, 11.2 ($p < 0.01$), AUC for TMMs 0.62 and 0.63 for HIMMs, Median CCI 14.0×10^9/L for HIMMs $\leq$ 3 vs. 11.2×10^9/L for HIMMs >3, $p < 0.01$, 13.5×10^9/L TMMs $\leq$ 9 vs. 11.2×10^9/L TMMs > 9, $p < 0.01$
Levin, 2004[36]	1-hr recovery—47% in patients with positive HLA antibody tests vs. 35% for patients with negative test ($p = 0.04$), 16-hr recovery—34% with positive HLA antibody tests vs. 15% with negative test ($p = 0.03$)
McFarland, 1989[37]	Correlation between PLT recovery at 1 hr and HLA match grade: median A vs. B1-B2 ($p < 0.05$), vs. B3-B4 ($p < 0.001$), vs. C ($p < 0.005$), vs. D ($p < 0.005$) Median B1-B2 vs. B3-B4 ($p < 0.02$), vs. D ($p < 0.07$) Correlation between PLT recovery at 18-24 hr and HLA-match grade: median A vs. B1-B2 ($p < 0.03$), vs. B3-B4 ($p < 0.001$), vs. C ($p < 0.001$), vs. D ($p < 0.0001$) Median B1-B2 vs. B3-B4 ($p < 0.05$), vs. D ($p < 0.02$) The effect of HLA seen only when LCT > 20%, clinical factors more important than HLA for 1-hr recovery and vice versa for 24-hr recovery by regression analysis
Heal, 1987[38]	CCI $\geq$ 7.5×10^9/L 33% for CXM+, 57% for CXM– ($p < 0.01$), A/BU 74%, BX 62%, C 51%, $p = 0.03$ for A/BU vs. C CXM most significant predictor of CCI vs. HLA and ABO, $p = 0.002$, HLA > ABO, $p = 0.02$
Klingemann, 1987[39]	5/71 (7%) refractory patients did not respond to HLA-matched PLTs
Levy, 1984[40]	Mean increment 33.0×10^9/L with HLA-matched PLTs
McElligott, 1982[41]	1-hr recovery for HLA Bw4/Bw6 compatible 84% vs. incompatible 52%, $p < 0.02$ 24-hr recovery for compatible 44% vs. incompatible 24%, $p < 0.01$
Daly, 1980[42]	For refractory patients (CCI < 10.0×10^9/L at 1 hr) CCI at 1 hr were 15.0×10^9/L with HLA-matched vs. 3.0×10^9/L with RDP ($p < 0.001$), For refractory patients (CCI<10.0 $\times$ 109/L at 1 hr) CCI at 18 hr were 9.0×10^9/L with HLA matched vs. 1.0×10^9/L with RDP ($p < 0.001$), For nonrefractory patients (CCI $\geq$ 10.0×10^9/L at 1 hr) CCI at 1 hr were 12 (5-22) with HLA matched vs. 13 (10-20) with RDP (p value NR), For nonrefractory patients (CCI $\geq$ 10.0×10^9/L at 1 hr) CCI at 18 hr were 4.0×10^9/L with HLA-matched vs. 3.0×10^9/L with RDP (p value NR)
Tosato, 1978[12]	12-20 hr CCI > 5.0×10^9/L HLA-A 61% vs. B1 41% vs. B2 49% vs. C 42% vs. D 43% ($p < 0.04$ for A vs. B1, B2, C, D)
Mittal, 1976[43]	PPR 44%-49% for matched vs. 15% unmatched, $p < 0.001$
Lohrmann, 1974[44]	Median 1-hr CCI: HLA A 15.0×10^9/L vs. B1 14.7×10^9/L, p = ns vs. B2 6.3×10^9/L, $p < 0.001$, B1 vs. B2, $p < 0.001$ Median 20-hr CCI: HLA A 12.5×10^9/L vs. B1 10.9×10^9/L p = ns, vs. B2 4.8×10^9/L, $p < 0.001$ vs. mismatch, $p < 0.001$, B1 vs. B2, $p < 0.005$, B1 vs. mismatch, $p < 0.001$, B2 vs. mismatch, $p < 0.001$

ASP = HLA antibody specificity prediction method; C1q = first complement component; CXM = crossmatch; EBM = epitope-based match; ELISA = enzyme-linked immunosorbent assay; EMMs = eplet amino acid mismatches; HIMMs = highly immunogenic mismatches; IgG = immunoglobulin G; IR = irradiated; LCT = lymphocytotoxicity assay; LCTABS = lymphocytotoxic antibodies; LIFT = lymphocyte immunofluorescence test; LR = leukoreduced; ns = not significant; NR = not reported; PIFT = PLT immunofluorescence test; PPR = percentage of PLT recovery; RDP = random-donor pooled PLTs; SDP = single-donor PLTs; SPRCA = solid-phase red blood cell adherence.

cross-match–incompatible PLTs ($p < 0.007$). Yet, in a study of 73 patients, HLA matching resulted in a CCI of at least 4.5×10^9/L after 24 hours in 42%, compared to 23% with cross-matched PLTs ($p < 0.05$; Table 4).[45]

There was a trend apparent for improved PLT increments with increased HLA grade in refractory patients in most studies. PLT increments were higher with HLA A matches than with progressively lower grades of matches although the degree of improvement in the PLT count increment was not consistent (Table S2).[21,27,34,37,44,45]

The use of HLAMatchmaker for HLA-matched PLTs has been analyzed in 108 patients with refractory thrombocytopenia.[17,22,47] The outcomes were reported as differences between triplet amino acid mismatches (TMM). Two studies reported a significant difference of 2×10^9/L in the 1-hour posttransfusion increment for TMM of nine or less compared to more than nine[17,47] and the third study only included nine patients.[22]

Data are inconsistent for the change in PLT increments with HLA-matched PLTs for patients with nonrefractory thrombocytopenia potentially because of the paucity of data, the timing of the PLT increment, and the measures used for the PLT increment, for example, CCI[42] compared to PLT recovery.[43] The presence of HLA antibodies correlated with the response to HLA-matched PLTs[36] with improved responses were observed with lower antibody grades[46] (Table 4). The degree of antigen mismatch was not associated with CCI but CCI was associated with the number of antigens shared.[31]

DISCUSSION

This is the first systematic review to examine the effects of HLA-matched PLT transfusion in patients with hypoproliferative thrombocytopenia. This review included data on several protocols for selecting of HLA-matched PLTs, including classical HLA matching, matching on the basis of CREGs, antigen avoidance, and HLAMatchmaker. HLA-matched products resulted in higher 1-hour posttransfusion increments compared to random-donor products in refractory patients. The significance of this increment with clinical outcomes has not been determined.

There was one RCT and 29 nonrandomized studies, with a combined sample size of approximately 1600 patients. The body of evidence consisted of mainly nonrandomized, single-center studies conducted in North America and involving hematological-oncologic adult patients who developed refractoriness to random-donor PLTs. The only controlled trial[23] involved nonrefractory patients and did not show significant differences in the number of bleeding episodes, rate of alloimmunization or refractoriness, posttransfusion PLT count increment, and PLT utilization between HLA matched and randomly selected products. Unfortunately, the study was not adequately powered to detect differences in any of the outcomes. Generally, the observational studies included small samples, used limited methodologically rigorous techniques (e.g., only 52% described eligibility criteria) and 62% were published before 1990. The current standards for detailing study design methods were not used (Table S3). For example, many studies lacked a control group, and very few included a predetermined sample size to detect a clinically significant difference. None of the studies performed blinded outcome assessments. Factors now known to significantly affect posttransfusion PLT counts, either product related including ABO PLT compatibility, product age, method of production or patient related including presence of fever, disseminated intravascular coagulation, antimicrobial medications, or splenomegaly[48,49] were not routinely analyzed; only 21% of studies accounted for confounding variables. Moreover, perhaps the most significant confounding variable in these studies assessing the effect of HLA matching was the absence of accounting for the use of leukoreduction, as leukoreduction has been shown to decrease the rates of both alloimmunization and PLT refractoriness.[10,11,50]

There was a paucity of data on the effect of HLA-matched PLT transfusions on clinical outcomes. For example, only two studies reported mortality outcomes. Of the four studies that reported bleeding outcomes, only one used a standardized reporting system for hemorrhage.[24] Having said that, bleeding is a notoriously difficult outcome to measure, and there are no validated and unambiguous bleeding grading criteria. Except for the RCT, these studies did not have an adequate control group, and frequently outcomes were reported for the entire patient population. As a result, we were unable to make any definitive conclusions on the effect of HLA matching on either mortality or bleeding. Alloimmunization and refractoriness were examined in one RCT, two prospective studies, and four retrospective studies. HLA-matched products led to decreased rates of both complications; however, it remains unclear whether they offer additional benefit beyond what is observed with leukoreduction alone. We could not demonstrate an impact of HLA matching on PLT utilization. There were no studies that described length of hospital stay, morbidity, or quality of life or included an economic or cost-effectiveness analysis.

The majority of the studies reported on the posttransfusion PLT increment, which was defined in a variety of ways including posttransfusion PLT CCI measured at 1 to 24 hours posttransfusion, percentage of PLT recovery at 1 to 24 hours, or percentage of successful transfusions defined as those transfusions that achieved a certain predefined increment. This heterogeneity has led to an inability to combine results in a meta-analysis. Many studies described better PLT increments with HLA-matched compared to random PLTs for patients with refractory thrombocytopenia after 1 hour; however, the results at 18 to 24 hours were variable. This suggests that

HLA-matched PLTs may have a reduced survival with clearance by 24 hours. The effect of HLA matching appeared less prominent in studies that utilized leukoreduced products and was more pronounced in studies involving nonleukoreduced PLTs. Seven studies[12,30,32,37,44-46] showed that closer HLA matches were associated with better increments except for one[38] that showed that crossmatch compatibility, rather than HLA (or ABO) matching, was the most significant predictor of posttransfusion CCI. The degree of antigen mismatch was not associated with CCI but CCI was associated with the number of antigens shared. HLA-matched PLTs appeared to produce better transfusion outcomes in patients with alloimmune refractoriness.[36]

We also found significant heterogeneity in definitions of alloimmunization, refractoriness, and PLT selection methods. Methods for diagnosing alloimmunization varied from lymphocytoxicity assays to such sensitive techniques as flow cytometry. The variability in the definition of refractoriness (Table S2) likely impacted the outcomes. Standardized definitions of alloimmunization, refractoriness, and what constitutes an adequate posttransfusion outcome (either count increment or percent recovery) are necessary to allow for comparisons. Moreover, the definition of HLA-"matched" PLT transfusions likely has changed over the years and this may have also impacted the outcomes. Methods for HLA matching varied widely and included conventional HLA matching, CREG matching, antibody specificity prediction, and use of the HLAMatchmaker. There were five studies[16,35,38,45,47] that compared some of these methods. However, no definite inferences can be made as to the superiority of one method compared to the others.

In conclusion, HLA-matched PLTs lead to improved transfusion outcomes defined as posttransfusion PLT count increments or percentage of PLT recovery at 1 hour. The responses to HLA-matched PLTs are better in those with evidence of alloimmune refractoriness and those receiving closer HLA-matched, antigen-negative products. We could not demonstrate any additional benefit of HLA matching in reduction of alloimmunization and refractoriness beyond leukoreduction. The major limitations of this review stem from the limitations of the existing data. The majority of reviewed literature was published before the year 2000 (only seven studies were published within the past 10 years) and utilized technology or methods that are infrequently used nowadays. Furthermore, the studies were performed with much less rigor than is currently expected by the scientific community. There was significant heterogeneity in definitions of outcomes precluding any meaningful comparisons or meta-analysis. The question of whether HLA-matched PLTs can result in better clinical outcomes, including bleeding frequency or severity, morbidity, or mortality, however, remains unanswered.

Despite the lack of convincing evidence, provision of HLA-matched PLTs for patients suspected or known to have alloimmune refractoriness remains a standard of care. It is a labor- and a time-intensive process that also requires a very large pool of dedicated and typed PLT donors as well as considerable investment of health care dollars. On the other hand, identifying donors with acceptable mismatches based on patients' antibody reactivity patterns may be an alternative approach that would potentially increase the donor pool. In this era of leukoreduction, pathogen reduction and new technologies that can precisely identify a specificity of an anti-HLA and match a product on the basis of antigen amino acid sequence, this is an opportune time to reexamine the utility of HLA matching. Ideally, we need a multicenter prospective trial comparing the most commonly used approaches powered to detect a difference in mortality or bleeding outcomes and include an economic analysis as well as quality-of-life assessments. If surrogate markers are to be reported, then we recommend to use CCI determined 1-hour posttransfusion as it will, arguably, best be able to differentiate between immune versus nonimmune refractoriness. Although a RCT would be optimal, an adequately conducted nonrandomized study using a propensity score method[51] to account for the various confounding variables that can affect outcomes may also address this question. Now that the gaps in our knowledge have been clearly illuminated, it is time to move forward.

CONFLICT OF INTEREST

There are no conflicts of interest. NS is consultant for Canadian Blood Services. Canadian Blood Services as a funding agency did not have any role in the design, analysis, and interpretation of the data or preparation, review, and approval of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Assessment of risk of bias in the randomized controlled trial.
Table S2. Characteristics of nonrandomized studies. (12,13,16,20-22,24-47)
Table S3. Quality of nonrandomized studies.
Appendix S1. Search strategy.
Appendix S2. Acknowledgments.