SUPPLEMENTARY APPENDIX

Treatments for hematologic malignancies in contrast to those for solid cancers are associated with reduced red cell alloimmunization

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Methods

Study period

The study period varied per hospital according to the electronic availability of necessary data: January 1, 2005 to December 31, 2010 at Leiden University Medical Center (Leiden), September 6, 2006 to December 31, 2013 at University Medical Center Utrecht (Utrecht), November 19, 2011 to December 31, 2013 at VU University Medical Center (Amsterdam), May 1, 2007 to April 30, 2013 at Catharina Hospital (Eindhoven), July 1, 2005 to December 31, 2013 at Jeroen Bosch Hospital ('s Hertogenbosch), and October 5, 2008 to December 31, 2013 at Haga Teaching Hospital (The Hague).

Eligibility criteria

Eligible patients received their first red cell transfusion within the study period in one of the six participating hospitals, provided the availability of at least one (negative) pre-, and one post-transfusion antibody screen.

For all identified cases, transfusion-induced alloimmunization was verified by the donors' and the patient's phenotypes. This in addition enabled us to discriminate allo- from autoimmunisation. Alloimmunized patients lacking exposure to a (documented or assumed) antigen-positive red cell unit were excluded. To prevent inclusion of boosting events, alloimmunizations detected within seven days of a first mismatched transfusion were excluded. By consulting the nationwide alloimmunization registry (TRIX),[1] we additionally excluded patients who were previously diagnosed with alloimmunization in other hospitals. Finally, hemoglobinopathy patients and infants below six months of age were not included. Although we were not informed on previous pregnancies in females, our study design sets out to minimize earlier pregnancy-induced alloimmunization as much as possible, as was recently discussed.[2]

Transfused products and detection of red cell alloantibodies

All transfused red cell units were buffy-coat depleted, subsequently filtered through a leukocyte depletion filter and stored in SAGM for a maximum of 35 days.[3]

Patients in the Netherlands are routinely screened for red cell alloantibodies sometime during the 72 hours prior to red cell transfusion. Antibody screening involves an indirect antiglobulin test (column agglutination technology from BioRad, Cressier, Switzerland, or from Ortho Clinical Diagnostics, Raritan NJ, United States). According to Dutch transfusion guidelines, commercially available 3-cell screening panels are homozygous positive for D, C, c, E, e, K, Fy^a, Fy^b, Jk^a, Jk^b, M, S and s. The K antigen needs to be present minimally heterozygously; the presence of C^w, Lu^a, Wr^a, and Kp^a is not

mandatory.[3] If positive, screening was followed by subsequent antibody identification by an 11-cell panel using the same technique.

Data acquisition and statistical analyses

We gathered routinely stored data on red cell transfusion dates, dates and results of antibody screens (including antibody specificity), patients' date of birth, sex, and leukocyte counts from the hospitals' electronic laboratory information systems. In addition, we examined the medical charts of all cases and controls for the presence of various potential clinical risk variables during the alloimmunization risk period, including (hemato-)oncological diagnoses and treatment modalities. The associations of hematological malignancies and solid cancers with the development of red cell alloimmunization were evaluated using conditional logistic regression models. For crude relative risk (RR) calculations, we conditioned on the matched variables i.e. hospital and cumulative number of red cell units received. To control for additional confounders, we first identified covariates as possible confounders of a given determinant, based on their observed association with this determinant among the source population (i.e. the non-alloimmunized controls).[4] Such an association was defined as a ≥3% difference in covariate presence between controls exposed and controls not exposed to a given determinant. Covariates in the causal pathway between the determinant and the outcome were not considered as confounders.[4] Second, to address missing data on these confounders, we used multiple imputation (see below). Third, to also accurately control for confounders with rare prevalences, we estimated a probability score for each determinant using logistic regression with the potential confounders as predictors.[5] Finally, we evaluated the association of various types of malignancies and treatment modalities with red cell alloimmunization by entering the corresponding probability scores next to the matching variables into the logistic regression model with alloimmunization as the outcome.

We next assessed the association between (the degree of) leukopenia and red cell alloimmunization. Missing leukocyte counts were similarly multiply imputed (see below). Minimum leukocyte counts were subcategorized into 2-4, 1-2 and <1x 10^9/L and referenced to normal counts (4-10x10^9/L). Since the likelihood that a low leukocyte count has been recorded at least once increases with the number of measurements and thus with the duration of hospitalization, we repeated this analysis limited to leukocyte counts measured within the week following the implicated transfusion.

A possible association between leukopenia (i.e. leukocyte counts <4x10^9/L) and type of malignancy was evaluated using Pearson's chi-square test.

As we used an incidence-density sampling procedure for selecting controls,[6] we interpreted and present all odds ratios as RR with 95% confidence intervals (CI).

Multiple imputation

To provide values for some missing predictor values, we performed multiple imputation creating five imputed datasets. Predictor variables included: alloimmunization status, age, gender, number of transfusions received, (types of) malignancies, chemo- and/or immunotherapy therapy, radiotherapy, use of immunosuppressant medication, (timing of) allogeneic and/or autologous stem cell transplant, graft versus host disease, (types of) infection, (duration of) fever, (duration of) ICU admittance, (types of) surgery, diabetes mellitus type 1, diabetes mellitus type 2, atherosclerosis, liver cirrhosis, renal insufficiency with a GFR ≤ 30 ml/min, dialysis, minimum leukocyte counts, maximum leukocyte counts, and maximum CRP values.

Table S1. Specificity and distribution of first-formed red cell alloantibodies according to the presence and type of malignancy.

Alloantibody specificity	All patients, N (%)	Acute leukemia or mature lymphoma, N (%)	Carcinoma (%)
anti-C	23 (4.0)	0 (0)	4 (3.1)
anti-c	41 (7.2)	0 (0)	6 (4.7)
anti-E	185 (32.3)	4 (20.0)	43 (33.3)
anti-e	5 (0.9)	0 (0)	1 (0.8)
anti-K	126 (22.0)	3 (15.0)	32 (24.8)
anti-C^w	19 (3.3)	1 (5.0)	4 (3.1)
anti-Fy^a	31 (5.4)	0 (0)	3 (2.3)
anti-Fy^b	5 (0.9)	0 (0)	1 (0.8)
anti-Jk^a	54 (9.4)	3 (15.0)	17 (13.2)
anti-Jk^b	7 (1.2)	2 (10.0)	0 (0)
anti-Le^a	7 (1.2)	2 (10.0)	2 (1.5)
anti-Le^b	3 (0.5)	0 (0)	1 (0.8)
anti-Lu^a	32 (5.6)	3 (15.0)	9 (7.0)
anti-Lu^b	0 (0)	0 (0)	0 (0)
anti-M	22 (3.8)	2 (10.0)	3 (2.3)
anti-N	1 (0.2)	0 (0)	0 (0)
anti-S	12 (2.1)	0 (0)	3 (2.3)
anti-s	0 (0)	0 (0)	0 (0)
All antibodies	573	20	129
(possibly) natural occurring *	268 (46.7)	12 (60.0)	62 (48.1)
generally not inducing hemoysis†	55 (9.6)	5 (25.0)	12 (9.3)
N patients	505	19	112
N patients with ≥ 2 first-time alloantibodies	63 (12.5)	1 (5.3)	15 (13.4)

* including: anti-E, anti-C^w, anti-Le^a, anti-Le^b, anti-Lu^a, and anti-M. † Including: anti-Lu^a, anti-M and anti-N. The distribution of (possibly) natural occurring antibodies did not significantly differ between patients with acute leukemia or mature lymphoma as compared to the remaining of the study population, including patients with carcinoma (p=0.09, chi square test). In contrast, the frequency of non-hemolytic alloantibodies was higher in alloimmunized patients

with acute leukemia or mature lymphoma as compared to the remaining of the immunized population (p=0.03), however, this did not affect conclusions presented in table 2 (data not shown).

Table S2. Diagnoses, treatments and complications present during the alloimmunization risk period.

Characteristics	Cases (N=505)	Controls (N=1010)	Missing
Patient diagnoses			
Diabetes mellitus (type 1 or 2)	97 (19.2)	183 (18.1)	1
GFR ≤ 30 ml/min *	56 (11.1)	149 (14.8)	
Atherosclerosis †	198 (39.5)	314 (31.5)	17
Chronic obstructive airway disease ‡	43 (8.5)	89 (9.0)	20
Splenectomy (in past or during risk period)	1 (0.2)	19 (1.9)	
Liver cirrhosis	13 (2.6)	24 (2.4)	2
Haematological malignancy	60 (11.9)	210 (20.8)	13
Carcinoma	112 (22.3)	183 (18.2)	7
Treatment interventions			
ICU admission	177 (36.5)	369 (35.0)	
Surgery	267 (52.9)	457 (45.2)	2
Organ transplant	4 (0.8)	23 (2.3)	
Dialysis (either chronic or acute) §	31 (6.1)	98 (9.7)	
Immunosuppressant medication ||	154 (30.9)	423 (42.4)	20
Chemotherapy ¶	66 (13.1)	224 (22.2)	6
Radiotherapy	15 (3.0)	37 (3.7)	
Stem cell transplant (autologous or allogeneic, in past or during risk period)	10 (2.0)	63 (6.2)	
Treatment related complications			
Leukopenia **	102 (20.2)	313 31.0)	
Graft versus host disease	4 (0.8)	15 (1.5)	3
Infections			
bacterial	142 (29.3)	275 (28.7)	72
viral	15 (3.0)	38 (3.8)	9
fungal	12 (2.4)	44 (4.4)	13

Values are n (%), unless otherwise stated. Numbers of patients with unavailable data per variable are presented as missing. IQR = interquartile range.

* glomerular filtration rate (GFR) below 30 ml/min during at least one week of the risk period (with GFR calculated using the Modification of Diet in Renal Diseases (MDRD) equation). † systemic or coronary atherosclerosis. ‡ chronic asthma bronchiale or chronic obstructive pulmonary disease. § hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration needed for at least one day during the risk period. || medication under subcategory H02 (corticosteroids) or L04 (other immunosuppressants) within the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification index. ¶ medication under subcategory L01 in the ATC classification index with the exception of agents in the subgroup L01XC (monoclonal antibodies) ** at least once measured leukocyte counts below lower limit of normal.

Table S3. Categories and types of malignancies present during the alloimmunization risk period.

Hematologic malignancies	**N**
Diagnosed in *N* patients	270
Acute leukemia	88
myeloid (AML)	76
lymphoblastic (ALL) *	12
Myelodysplastic syndrome	63
Multiple myeloma	36
Myeloproliferative neoplasm	38
Chronic lymphatic leukemia	12
Lymphoma	40
(mature) B-cell lymphoma †	32
T-cell lymphoma ‡	7
undifferentiated	1

Other	**N**
Diagnosed in *N* patients	43
Germ cell tumors	4
Melanoma	1
Neuro-endocrine tumors	3
Stromal and mesenchymal neoplasms	35

Carcinomas	**N**
Diagnosed in *N* patients	295
Adrenal	2
Bile tract	2
Breast	21
Cervix, endometrial	14
Colorectal	71
Duodenal, stomach	15
Esophagus	11
Head and neck	17
Hepatic cell	6
Lung §	41
Ovarian	19
Pancreatic	7
Prostate	21
Renal cell	20
Squamous cell	3
Unknown primary origin ||	3
Urothelial	20
Vaginal, vulvar	2
Other	1

Cumulative numbers of types of malignancies per category may exceed the number of patients per category, as some patients were diagnosed with two malignant diseases.

* acute lymphoblastic leukemia and acute lymphoblastic lymphoma. † of which: 6 patients with Burkitt lymphoma, 11 with diffuse large B cell lymphoma, 5 with follicular lymphoma, 1 with hairy cell lymphoma, 4 with Hodgkin lymphoma, 3 with mantle cell lymphoma, 1 with low-grade B cell lymphoma not otherwise specified, and 1 with lymphoplasmacytic lymphoma. ‡ of which: 3 patients with anaplastic T cell lymphoma, 1 with mycosis fungoides, and 3 with peripheral T cell lymphoma not otherwise specified. One patient was diagnosed with an undifferentiated mature lymphoma. § of which 37 patients with non-small cell lung carcinoma and 4 with small cell lung carcinoma. || of which: 2 patients with adenocarcinoma with unknown primary and 1 with squamous cell carcinoma with unknown primary.

Table S4 Characteristics of 1,010 non-alloimmunizated sampled controls during the alloimmunization risk period according to the presence and type of a malignancy.

Characteristics	Acute leukemia		Lymphoma		Carcinoma	
	present (N=74)	not present (N=935)	Present (N=35)	not present (N=973)	Present (N=183)	not present (N=822)
General						
Men	46 (62.2)	522 (55.8)	25 (71.4)	542 (55.7)	102 (55.7)	463 (56.3)
Age in years (median, IQR)	55.1 (37.6-65.5)	66.2 (52.5-75.8)	57.3 (34.3-67.1)	65.5 (52.0-75.4)	67.7 (58.5-75.9)	64.0 (49.3-74.9)
Transfused in university hospitals	42 (56.8)	421 (45.0)	20 (57.1)	444 (45.6)	62 (33.9)	400 (48.9)
Cumulative (lifetime) number of red cell units received (median, IQR)	6.0 (3.0-12.5)	4 (2-8)	3.0 (2.0-7.0)	4.0 (2.0-8.0)	3.0 (2.0-6.0)	4.0 (2.0-8.0)
Cumulative number of red cell units during risk period (median, IQR)	7 (4-11)	4 (2-8)	3 (2-6)	4 (2-8)	3 (2-6)	5 (3-9)
Days transfused during risk period (median, IQR)	3 (2-5)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-2)	2 (1-3)
Patient diagnoses						
Diabetes mellitus type 1	0 (0)	7 (0.87	1 (2.9)	6 (0.6)	1 (0.5)	6 (0.7)
Diabetes mellitus type 2	7 (9.5)	169 (18.1)	2 (5.7)	173 (17.8)	31 (16.9)	145 (17.6)
GFR ≤ 30 ml/min *	3 (4.1)	146 (15.6)	3 (8.6)	146 (15.0)	21 (11.5)	128 (15.6)
Atherosclerosis †	7 (9.5)	307 (32.8)	1 (2.9)	312 (32.1)	44 (24.0)	269 (32.7)
Chronic obstructive airway disease ‡	3 (4.1)	86 (9.2)	2 (5.7)	86 (8.8)	14 (7.7)	75 (9.1)
Splenectomy (in past or during risk period)	0 (0)	19 (2.0)	0 (0)	19 (2.0)	3 (1.6)	16 (1.9)
Liver cirrhosis	0 (0)	24 (2.6)	0 (0)	24 (2.5)	4 (2.2)	20 (2.4)
Malignancies						
acute leukemia	n.a.	n.a.	0 (0)	74 (7.6)	0 (0)	74 (9.0)
myelodysplastic syndrome	3 (4.1)	43 (4.6)	1 (2.9)	45 (4.6)	0 (0)	46 (5.6)
multiple myeloma	0 (0)	26 (2.8)	0 (0)	26 (2.7)	0 (0)	26 (3.2)
myeloproliferative neoplasm	0 (0)	29 (3.1)	0 (0)	29 (3.0)	0 (0)	29 (3.5)
chronic lymphocytic leukemia	0 (0)	7 (0.8)	0 (0)	7 (0.7)	0 (0)	7 (0.9)
Lymphoma	0 (0)	35 (3.7)	n.a.	n.a.	1 (0.5)	34 (4.1)
Carcinoma	0 (0)	183 (19.6)	1 (2.9)	182 (18.7)	n.a.	n.a.
Treatment interventions						

ICU admission	5 (6.8)	364 (38.9)	4 (11.4)	364 (37.4)	51 (27.9)	318 (38.7)
days at ICU (median, IQR)	0 (0-0)	0 (0-4.5)	0 (0-0)	0 (0-4)	0 (0-1)	0 (0-5)
Surgery						
thoracic including CABG	0 (0)	144 (15.4)	0 (0)	143 (14.7)	13 (7.1)	131 (15.9)
abdominal	1 (1.4)	180 (19.3)	0 (0)	181 (18.6)	55 (30.1)	126 (15.3)
back or spinal cord	0 (0)	11 (1.2)	0 (0)	11 (1.1)	1 (0.5)	10 (1.2)
Organ transplant	0 (0)	23 (2.5)	0 (0)	23 (2.4)	0 (0)	23 (2.8)
Dialysis (either chronic or acute) §	1 (1.4)	97 (10.4)	1 (2.9)	97 (10.0)	8 (4.4)	90 (10.9)
Immunosuppressant medication ||	33 (44.6)	389 (41.6)	26 (74.3)	395 (40.6)	64 (35.0)	358 (43.6)
Chemotherapy ¶	64 (86.5)	155 (16.6)	28 (80.0)	191 (19.6)	39 (21.3)	180 (21.9)
Radiotherapy	0 (0)	39 (4.2)	4 (1.1)	35 (3.6)	21 (11.5)	18 (2.2)
HSCT (autologous or allogeneic, in past or during risk period) **	1 (1.4)	63 (6.7)	6 (17.1)	58 (6.0)	0 (0)	64 (7.8)
Treatment related complications						
Infections						
severe bacterial	4 (5.4)	165 (17.6)	2 (5.7)	166 (17.1)	33 (18.0)	135 (16.4)
Gram-negative bacteremia ††	6 (8.1)	38 (4.1)	2 (2.9)	42 (4.3)	9 (4.9)	35 (4.3)
disseminated viral ‡‡	0 (0)	20 (2.1)	2 (2.9)	18 (1.8)	0 (0)	20 (2.4)
Leukopenia §§	56 (75.7)	251 (26.8)	28 (80.0)	278 (28.6)	41 (22.4)	266 (32.3)

Values are n (%), unless otherwise stated. IQR = interquartile range. n.a. = not applicable. The presence of acute leukemia, mature lymphoma, and carcinoma could not be determined for one, two, and five control patients, respectively.

* glomerular filtration rate (GFR) below 30 ml/min during at least one week of the risk period (calculated according to the Modification of Diet in Renal Diseases (MDRD) equation). † systemic or coronary atherosclerosis. ‡ chronic asthma bronchiale or chronic obstructive pulmonary disease. § hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration needed for at least one day during the risk period. || medication under subcategory H02 (corticosteroids) or L04 (other immunosuppressants) within the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification index. ¶ medication under subcategory L01 in the ATC classification index with the exception of agents in the subgroup L01XC (monoclonal antibodies) ** hematopoietic stem cell transplant. ††abscesses, cardiac infections, infected foreign material, intra-abdominal infections, lower respiratory tract infections, meningitis, osteomyelitis, soft tissue infections, spondylodiscitis, upper urinary tract infections. ‡‡ viremia and varicella zoster infections. §§ at least once measured leucocyte counts below lower limit of normal.

Table S5. Subset of variables identified as confounders per determinant for alloimmunization .

Determinant	Confounders
all	Age, gender, (duration of) ICU admittance, thoracic surgery, atherosclerosis, GFR ≤ 30 ml/min, dialysis.
acute leukemia	Idem as under 'all', plus: abdominal surgery, DM2, COPD, MPN, lymphoma, carcinoma
Myelodysplastic syndrome	Idem as under 'all', plus: abdominal surgery, DM2.
Multiple myeloma	Idem as under 'all', plus: abdominal surgery, DM2, acute leukemia, lymphoma, carcinoma.
Myeloproliferative neoplasm	Idem as under 'all', plus: abdominal surgery, COPD, lymphoma, carcinoma.
Chronic lymphocytic leukemia	Idem as under 'all', plus: abdominal surgery, DM2, COPD, acute leukemia, MDS, lymphoma, carcinoma.
Lymphoma	Idem as under 'all', plus: abdominal surgery, DM2, COPD, acute leukemia, MPN, carcinoma.
Carcinoma	Idem as under 'all', plus: abdominal surgery, acute leukemia, MDS, MM, MPN, lymphoma.
Other malignancies	Idem as under 'all', plus: abdominal surgery, back or spinal surgery, splenectomy in past or during risk period, acute leukemia, MDS, lymphoma, carcinoma.
Chemo-/immunotherapy	Idem as under 'all', plus: abdominal surgery, DM2, COPD, immunosuppressant medication, acute leukemia, MDS, MM, MPN, lymphoma, carcinoma.
Radiotherapy	Idem as under 'all', plus: DM2, COPD, acute leukemia, MM, lymphoma, chemo-/immunotherapy, carcinoma.
Autologous stem cell transplant	Idem as under 'all', plus: abdominal surgery, DM2, COPD, acute leukemia, MM, MPN, lymphoma, carcinoma.
Allogeneic stem cell transplant	Idem as under 'all', plus: abdominal surgery, DM2, COPD, acute leukemia, MM, MPN, lymphoma, , carcinoma, (timing of previous) autologous HSCT.
(degree of) leukopenia	Idem as under 'all', plus: abdominal surgery, DM2, COPD, immunosuppressant medication, acute leukemia, MDS, MM, carcinoma, chemo-/immunotherapy, radiotherapy, (timing of) HSCT.

All determinants were associated with the variables listed under 'all'. In addition to these, several other potential confounders were identified per determinant.

Atherosclerosis = systemic or coronary atherosclerosis. GFR = glomerular filtration rate (GFR) below 30 ml/min during at least one week of the risk period (calculated according to the Modification of Diet in Renal Diseases (MDRD) equation. Dialysis = hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration needed for at least one day during the risk period. DM2 = diabetes mellitus type 2. COPD = chronic asthma bronchiale or chronic obstructive pulmonary disease. MDS = myelodysplastic syndrome. MPN = myeloproliferative neoplasm. MM = multiple myeloma. Immunosuppressant medication = medication under subcategory H02 (corticosteroids) or L04 (other immunosuppressants) within the Anatomical Therapeutic Chemical (ATC) classification index. Chemo-/immunotherapy = medication under subcategory L01 within the ATC index plus antithymocyte globulin. HSCT = hematopoietic stem cell transplant.

Table S6. Overview of imputed data per recorded variable.

Variable	Type of variable (C / D)	Missing, N (%)	Variable	Type of variable (C / D)	Missing, N (%)
Age	C	0 (0)	Multiple myeloma	C+D	0 (0)
Gender	C	0 (0)	Myeloproliferative neoplasm	C+D	4 (0.3)
(duration of) ICU admittance	C	4 (0.3)	Chronic lymphatic leukemia	D	0 (0)
Thoracic surgery	C	0 (0)	(Mature) lymphoma	C+D	3 (0.2)
Abdominal surgery	C	0 (0)	Carcinoma	C+D	7 (0.5)
Surgery of back or spinal cord	C	0 (0)	Chemo-/immunotherapy	C+D	8 (0.5)
Diabetes mellitus type 2	C	1 (0.1)	Radiotherapy	C+D	0 (0)
Atherosclerosis	C	17 (1.1)	Autologous HSCT (in past or during risk period)	C+D	0 (0)
COPD	C	20 (1.3)			
GFR ≤ 30 ml/min	C	2 (0.1)	Allogeneic HSCT (in past or during risk period)	C+D	0 (0)
Dialysis	C	0 (0)			
Splenectomy (in past or during risk period)	C	0 (0)	Use of immunosuppressant medication	C+D	20 (1.3)
Acute leukemia	C+D	1 (0.1)	Minimum leukocyte counts	D	41 (2.7)
Myelodysplastic syndrome	C+D	3 (0.2)			

Only missing data on variables assessed as determinants (D) of alloimmunization and potential confounders (C) of these determinants (table S3) are presented.

Atherosclerosis = systemic or coronary atherosclerosis. COPD = chronic asthma bronchiale or chronic obstructive pulmonary disease. GFR ≤ 30 ml/min = glomerular filtration rate below 30 ml/min during at least one week of the risk period (calculated according to the Modification of Diet in Renal Diseases (MDRD) equation). Dialysis = hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration needed for at least one day during the risk period. Chemo-/immunotherapy = medication under subcategory L01 within the ATC index plus antithymocyte globulin. HSCT = hematopoietic stem cell transplant. Immunosuppressant medication = medication under subcategory H02 (corticosteroids) or L04 (other immunosuppressants) within the ATC index.

Table S7. Association between non-hematological malignancies and red cell alloimmunization according to specific type of malignancies.

	Cases (N=505)	Controls (N=1,010)	RR (CI) *	Adjusted RR (CI) †	Excluded from analysis
Carcinoma	112 (22.3)	183 (18.2)	1.30 (0.99-1.70)	1.01 (0.75-1.37)	7
Breast	8 (1.6)	13 (1.3)	1.30 (0.53-3.18)	1.02 (0.40-2.58)	0
Colorectal	24 (4.8)	47 (4.7)	1.08 (0.64-1.81)	0.86 (0.49-1.49)	0
Lung	17 (3.4)	24 (2.4)	1.47 (0.77-2.78)	1.22 (0.63-2.37)	0
Prostate	4 (0.8)	16 (1.6)	0.53 (0.17-1.61)	0.49 (0.16-1.53)	0
Renal cell	6 (1.2)	14 (1.4)	0.91 (0.35-2.41)	0.83 (0.31-2.23)	0
Urothelial	7 (1.4)	13 (1.3)	1.11 (0.44-2.84)	1.09 (0.41-2.89)	0
Other	12 (2.4)	31 (3.1)	0.77 (0.39-1.53)	0.83 (0.41-1.68)	1
Stromal and mesenchymal	9 (1.8)	26 (2.6)	0.69 (0.31-1.50)	0.74 (0.33-1.65)	1

Values are n (%). Only subtypes of solid tumors with at least 20 patients diagnosed are presented. * Adjusted for the matched variables: number of transfused red cell units and hospital. † Additionally adjusted for other potential confounders (for details, see appendix p 10-11).

Table S8. Chemotherapy and red cell alloimmunization risks.

Type of malignancy	Chemotherapy	Cases (N=505)	Controls (N=1,010)	RR (CI) *	Adjusted RR (CI) †
Multiple myeloma					
-		493	981	*ref*	*ref*
+	-	4	7	1.14 (0.32-4.06)	1.19 (0.33-4.34)
+	+	6	18	0.67 (0.26-1.72)	0.70 (0.27-1.82)
Myeloproliferative neoplasm					
-		494	977	*ref*	*ref*
+	-	3	13	0.46 (0.13-1.63)	0.48 (0.13-1.73)
+	+	6	16	0.75 (0.29-1.95)	0.79 (0.30-2.09)
Chronic lymphatic leukemia					
-		499	999	*ref*	*ref*
+	-	1	3	0.49 (0.05-4.85)	0.67 (0.07-6.47)
+	+	3	4	1.27 (0.27-6.01)	1.53 (0.33-7.11)

+ = present; - = absent. Only numbers of patients for whom the presence or absence of a given malignancy and the use of chemotherapy during the alloimmunization risk period could be determined are presented. * Adjusted for the matched variables: number of transfused red cell units and hospital. † Additionally adjusted for other potential confounders (for details, see appendix p 10-11).

Table S9. Types of chemotherapeutic agents per drug category with their associated sample numbers.

Drug category and name	Number of patients	Drug category and name	Number of patients
Alkaloid		**Hypomethylating agents**	
Vincristine	31	Azacitidine	7
Vinorelbine	1	Decitabine	1
Alkylating agents		**Platinum-based agents**	
Busulfan	10	Carboplatin	20
Carmustine	3	Cisplatin	41
Chlorambucil	4	Oxaliplatin	5
Cyclophosphamide	34	**Proteinkinase inhibitors**	
Ifosfamide	8	Dasatinib	4
Lomustine	2	Imatinib	6
Melphalam	15	Nilotinib	1
Thiotepa	1	Sunitinib	1
Antimetabolites		**Other**	
Capecitabine	12	Amsacrine	11
Clofarabine	10	(peg)-asparaginase	9
Cytarabine	80	Bortezomib	8
Fludarabine	23	Hydroxycarbamide	21
Fluorouracil	2	Mitotane	1
Gemcitabine	16	Procarbazine	1
Mercaptopurine	8	Tretinoin	4
Methotrexate	28	**Taxane**	
Pemetrexed	9	Docetaxel	7
Thioguanin	4	Paclitaxel	9
Anthracyclines		**Topo-isomerase inhibitors**	
Daunorubicin	21	Etoposide	39
Doxorubicin	26	Irinotecan	1
Epirubicin	5		
Idarubicin	28		
Mitoxantrone	8		

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