Predictive Calculation of Effectiveness of a Regional Bone Marrow Donor Registry in Vojvodina, Serbia

Svetlana Vojvodić[1] and Stevan L. Popović[2]

[1] Department for Immunoserological and Immunogenetical Investigation, Institute for Blood Transfusion Novi Sad, Novi Sad, Serbia
[2] Department of Hematology, Institute of Internal Medicine, Novi Sad, Serbia

ABSTRACT

The aim of this study was to determine the percentages of patients from Vojvodina who would find at least one HLA identical unrelated donor in various sizes of donor files. To determine the probability that 200 patients will have given phenotype, we defined three-locus haplotype frequencies through the phenotype frequencies of HLA A,B and DR antigens as well as observed AB and BDR haplotype frequencies. Then we calculated the percentages of patients theoretically able to have at least one HLA identical donor in a donor file of a certain size. According to the results of a study sample, predictive estimation of the effectiveness of regional bone marrow donor registry in Vojvodina, would be 14% with 5,000 donors, 23% with 10,000 donors, 38.5% with 20,000 donors, 49.5% with 30,000 donors and 76% with 100,000 donors in the registry. The appropriate size of registered donor file that would give at least one HLA identical donor for more than 45% of patients from Vojvodina is 30,000 donors.

Key words: *bone marrow, unrelated donors, effectiveness, percentage chart, Vojvodina, Serbia*

Introduction

In recent years bone marrow and haematopoietic stem cell (BM/HSC) transplantation has been used as a curative treatment for patients who have severe aplastic anemia, some forms of leukemia, myelodysplastic syndrome or other diseases. The most desirable donors, a HLA identical sibling is available for only approximately one third of candidates for BM/HSCT[1–6]. Since, the results of BMT with usage HLA nonidentical relatives have not been satisfactory[7,8], attention has turned to nonrelated HLA identical donors or donors compatible for et least five of six HLA-A,B and -DR antigens[9–13]. However, it is very difficult to find HLA compatible donors from an unrelated population because HLA system is highly polymorphic; a large file would be necessary. To increase the availability of unrelated donors, national registries like the National Marrow Donor Program in the USA and the Anthony Nolan registry in the United Kingdom, have been started to satisfy the need of donors for unrelated bone marrow transplantation[14,15]. Even in the largest registries, finding a donor for an individual patient could be impossible[14,16,17]. In such cases investigating the possibility of finding donors abroad is necessary, so for that purpose, the Bone Marrow Donor Worldwide registry has been set up[3,6,14,18–20].

To determine and evaluate theoretically the appropriate size of the donor file in the population of Vojvodina, we calculated three-locus haplotype frequencies and phenotype frequencies for 200 patients. Then we calculated the probability of finding at least one HLA identical donor among k randomly chosen donors. We further evaluated the percentages of potential BM/HSCT recipients for whom at least one HLA identical donor could be found among a variable of unrelated donor candidates with assumption that the bigger donor pool size provides the higher effectiveness of a registry.

Received for publication August 28, 2005

Material and Methods

We applied immunomagnetic technique (IM) in HLA class I and II antigens typing for 200 patients from Vojvodina who suffer from leukaemia and myelodysplastic syndrome[21]. We obtained the AB and BDR haplotype frequencies through direct counting method. Gene frequencies were calculated using following formula:

$$P_A = 1 - \sqrt{1 - f_A},$$

where f_A is phenotype frequency of the certain allele[22].

Three locus haplotype frequencies were calculated by Piazza's formula:

$$PA_1B_1DR_1 = \frac{P(A_1B_1)(B_1DR_1)}{B_1},$$

where P (A_1B_1) and (B_1DR_1) are observed haplotype frequencies[23].

The frequency of the phenotype $P(A_1A_2B_1B_2DR_1DR_2)$ was calculated by following formula: $P_1=\Sigma Q(A_1B_1DR_1)\times Q(A_2B_2DR_2)$, where the summation is divided by all possible combinations of the haplotypes that yield the phenotype under consideration[6]. In the case of homozygosity at a locus, procedure takes into account extra haplotypes that have an undetected antigen on these loci[24]. The probability of finding at least one phenotypic match among k randomly chosen donors was calculated by utilizing formula: $P=1-(1-pD_i)^k$, where pD_i is the frequency of a patient's phenotype[16]. Considering the number of k randomly chosen donors that provide at least one phenotypic match for 200 patients from Vojvodina, we estimated the percentages of patients theoretically able to have at least one HLA identical donor in a donor file of a certain size. The apropriate number of k randomly choosen donors, was gradualy increased with an aim to achieve 99.99% probability of finding compatibile donor that is in accordance with the HLA phenotypic frequencies of the racipients. From the percentages of patients with HLA identical donor in the various sizes of donor files, we draw the connection between the required donor file size and the percentages of patients who will have possible unrelated matched donors. Then we tried to determine the appropriate size of registered donor file that will give at least one HLA identical donor for more than 45 per-

TABLE 1
PHENOTYPE FREQUENCIES OF HLA A, B AND DR ANTIGENS

A locus	af		gf		B locus	af		gf		DR locus	af		gf	
A1	0.33		0.181		B5	0.145		0.075		DR1	0.185		0.097	
A2	0.54		0.321		B5(51)	0.13	0.285	0.067	0.154	DR2	0.215		0.114	
A3	0.155		0.08		B5(52)	0.01		0.005		DR2(15)	0.155	0.375	0.08	0.209
A9	0.05		0.025		B7	0.115		0.059		DR2(16)	0.005		0.002	
A9(23)	0.005	0.22	0.002	0.116	B8	0.19		0.1		DR3	0.2		0.105	
A9(24)	0.165		0.086		B12	0.01		0.005		DR3(17)	0.005	0.21	0.002	0.111
A10	0.07		0.035	0.088	B12(44)	0.1	0.115	0.051	0.059	DR3(18)	0.005		0.002	
A10(25)	0.035	0.17	0.017		B12(45)	0.005		0.002		DR4	0.155		0.08	
A10(26)	0.065		0.033		B13	0.06		0.03		DR5	0.03		0.015	
A11	0.11		0.056		B14	0.09		0.046		DR5(11)	0.285	0.33	0.154	0.181
A28	0.03		0.015		B15	0.05		0.025		DR5(12)	0.015		0.07	
A29	0.005		0.002		B16	0.06		0.03		DR6	0.01		0.005	
A30	0.03		0.015		B16(38)	0.05	0.12	0.025	0.061	DR6(13)	0.06	0.085	0.03	0.043
A31	0.005		0.002		B16(39)	0.01		0.005		DR6(14)	0.016		0.008	
A32	0.04		0.02		B17	0.07		0.035		DR7	0.14		0.072	
A33	0.035		0.017		B18	0.155		0.08		DR8	0.035		0.017	
A34	0.005		0.002		B21	0.07		0.035		DR9	0.015		0.007	
Bla	0.325		0.178		B22	0.03		0.015		DR10	0.035		0.017	
					B27	0.095		0.048		Bla	0.435		0.248	
					B35	0.165		0.086						
					B37	0.02		0.01						
					B40	0.05		0.025						
					B41	0.015		0.007						
					B47	0.005		0.002						
					B48	0.005		0.002						
					Bla	0.295		0.160						

af – antigen frequencies, gf – genes frequencies, Bla – blank

TABLE 2
OBSERVED AB AND BDR HAPLOTYPE FREQUENCIES

Haplo-type	B5	B51	B52	B7	B8	B12	B44	B45	B13	B14	B15	B16	B38	B39	B17	B18	B21	B22	B27	B35	B37	B40	B41	B47	B48	Bla
A1	0.055	0.04	/	0.035	0.155	0.005	0.02	/	0.015	0.02	/	0.015	0.015	/	0.025	0.03	0.015	0.005	0.01	0.08	0.01	0.02	/	/	/	0.08
A2	0.105	0.095	0.005	0.035	0.08	0.01	0.015	0.005	0.035	0.04	0.025	0.04	0.025	0.01	0.035	0.07	0.045	0.015	0.07	0.065	0.015	0.025	0.01	0.01	/	0.145
A3	0.01	0.01	/	0.05	0.035	/	0.015	/	0.015	0.02	0.01	0.005	0.005	/	0.01	0.03	0.01	0.005	0.005	0.03	/	0.015	/	/	/	0.04
A9	0.005	0.005	/	0.01	0.005	0.005	0.005	/	0.005	0.005	/	/	/	/	/	0.005	0.015	0.01	0.005	0.005	/	0.005	/	/	/	0.01
A23	/	/	/	/	/	/	/	/	/	/	0.005	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0.005
A24	0.01	0.035	/	0.015	0.02	/	0.03	/	0.005	0.005	0.01	0.005	0.005	/	0.015	0.035	/	/	0.03	0.02	0.005	0.01	0.005	/	0.005	0.06
A10	0.005	0.01	/	0.005	0.015	/	0.005	/	/	0.01	0.005	0.02	0.01	/	/	0.01	/	0.005	0.005	0.005	/	0.005	0.005	/	0.005	0.02
A25	0.005	0.005	/	0.005	0.005	/	/	/	/	/	0.005	/	/	/	0.005	0.02	0.005	/	0.005	/	/	/	/	/	/	0.01
A26	0.005	0.01	0.005	0.01	/	/	/	/	0.005	0.005	/	/	0.02	0.005	/	0.005	0.005	0.005	/	0.02	/	/	/	0.005	/	0.025
A11	0.005	0.005	0.005	/	0.015	/	0.02	/	/	0.01	0.01	0.005	/	/	0.015	0.025	0.005	0.005	0.015	0.035	/	0.015	/	/	/	0.03
A28	0.005	0.005	0.005	0.005	0.015	/	/	/	/	0.005	/	0.005	0.005	/	/	/	/	/	/	0.01	/	/	/	/	/	/
A29	0.005	/	/	/	0.005	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
A30	/	0.005	/	0.005	/	/	0.005	/	0.01	0.005	0.01	/	/	/	/	/	0.005	/	/	0.01	/	/	/	/	/	0.005
A31	/	/	/	/	/	/	/	/	/	/	0.005	/	0.005	/	/	/	/	/	/	/	/	/	/	/	/	/
A32	0.015	0.005	/	0.015	/	/	0.005	/	0.005	/	/	/	0.005	/	/	/	0.005	/	0.005	0.01	/	/	/	/	/	0.01
A33	/	/	/	/	0.005	/	/	0.005	/	0.03	/	/	/	/	0.005	/	/	/	0.005	0.005	0.005	/	0.005	/	/	0.005
A34	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0.005	/	/	/	/	/	/	/	/	0.005	/
Bla	0.055	0.03	/	0.04	0.02	/	0.035	/	0.025	0.025	0.015	0.02	0.005	0.005	0.03	0.075	0.03	0.01	0.035	0.035	0.005	0.005	0.005	/	/	0.145
DR1	0.015	0.02	0.005	0.015	0.015	0.005	0.015	0.005	0.005	0.04	/	0.005	0.01	/	0.015	0.03	0.01	0.005	0.015	0.055	0.005	0.015	0.005	/	/	0.06
DR2	0.035	0.035	0.01	0.035	0.015	0.005	0.04	/	0.005	0.02	0.01	0.025	0.005	/	0.015	0.035	0.005	0.01	0.02	0.025	0.01	/	/	/	/	0.07
DR15	0.035	0.01	/	0.035	0.045	/	0.01	/	0.005	/	0.005	0.015	0.015	/	0,005	0.02	0.01	0.01	0.01	0.02	/	0.01	/	/	/	0.04
DR16	/	/	/	/	/	/	0.005	/	0.005	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
DR3	0.015	0.025	/	0.025	0.135	/	0.005	/	/	0.02	0.005	0.015	0.01	/	0.015	0.03	0.015	0.01	0.01	0.015	0.005	0.005	/	/	0.005	0.035
DR17	/	/	/	/	/	/	/	/	/	0.005	/	/	/	/	/	/	/	/	0.005	/	/	/	/	/	/	/
DR18	/	/	/	/	0.005	/	/	/	0.005	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
DR4	0.02	0.03	0.005	0.01	0.035	/	0.01	/	0.01	0.005	0.005	0.015	0.01	0.01	/	0.02	0.02	0,005	0.015	0.015	/	0.015	0.005	/	0.005	0.05
DR5	0.01	0.005	/	0.005	0.01	/	0.005	/	/	0.005	/	/	/	/	/	/	/	/	/	0.01	/	/	/	/	/	0.01
DR11	0.04	0.035	/	0.025	0.03	0.005	0.025	/	0.005	0.01	0.025	0.01	0.015	0.01	0.005	0,07	0.015	0.015	0.055	0.06	0.005	0.015	0.005	/	/	0.09
DR12	0.005	/	/	/	/	/	0.005	/	/	0.005	0.005	/	/	/	/	/	/	/	0.005	/	/	/	/	/	/	0.005
DR6	/	0.01	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0.005	/	/	/	/	/	/	/	/	0.005
DR13	0.02	0.005	/	0.01	0.01	/	0.01	/	0.01	/	0.005	0.005	0.005	/	0.005	/	/	/	0.015	0.01	/	/	/	0.005	/	0.005
DR14	0.005	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0.005	0.005	/	0.005	/	/	0.005	/	/	/	0.005
DR7	0.015	0.02	/	/	0.02	/	0.015	/	0.045	0.005	0.005	0.005	/	/	0.04	0.02	0.005	/	0.01	0.04	/	0.005	0.005	/	/	0.025
DR8	/	0.005	/	0.005	0.01	/	/	/	0.005	/	0.005	/	0.005	/	0.01	0.005	/	0.005	/	0.005	/	/	/	/	/	0.01
DR9	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0.005	0.01	/	/	/	0.005	/	/	0.01	0.005	0.005
DR10	/	/	/	0.01	0.01	0.005	0.005	/	/	0.005	/	0.005	0.005	/	/	0.005	/	/	/	0.005	0.005	/	/	/	/	0.005
Bla	0.05	006	/	0.055	0.04	/	0.065	0.005	0.02	0.03	0.03	0.02	0.02	/	0.03	0.065	0.04	/	0.04	0.08	0.005	0.025	0.01	/	/	0.175

Bla – blank

TABLE 3
PROBABILITY OF PHENOTYPE OCCURENCE AND NUMBER OF NECESSARY DONORS

pp	op/nd	pp	op/nd	pp	op/nd	pp	op/nd
A32,XB35,XDR5,7	0.000144199 140,000	A1,2B5(51),8DR3,5(11)	0.007664117 2,650	A2,30B14,21DR4,X	0.000114281 180,000	A2,10(25)B5(51),27DR1,7	0.000051416 400,000
A1,33B17,35DR1,6(13)	0.000035396 570,000	A2,30B5(51),35DR4,X	0.000276879 73,000	A1,2B5,12(44)DR1,X	0.000721549 28,000	A9(24),XB12(44),18DR5(11),7	0.000762739 2,000
A2,XB18,41DR5(11),X	0.001905322 10,800	A1,9(24)B8,18DR5(11),X	0.00271723 7,500	A2,XB21,XDR5(11),X	0.006160568 3,300	A1,2B5(51),21DR4,6	0.000208491 97,000
A2,10(26)B16(38),47DR6(13),X	0.00035 58,000	A11,XB21,22DR2(15),3	0.000039282 520,000	A2,9(24)B5(51),17DR3,7	0.000757141 27,000	A2,XB5(51),XDR2,5	0.009548307 2,100
A2,XB12(44),16(39)DR4,5(11)	0.00031625 65,000	A28,32B5(51),7DR1,X	0.00002642 780,000	A3,XB18,35DR1,2	0.000624982 33,000	A2,9(24)B5,41DR4,7	0.000100572 200,000
A2,33B12(45),14DR1,X	0.000611097 33,000	A28,10(26)B51,52DR2,4	0.000053844 380,000	A2,28B5,16DR2,X	0.0004306 47,000	A2,10(25)B18,21DR2,3	0.000222233 92,000
A2,XB22,27DR2,5(11)	0.001135963 18,000	A1,XB8,18DR3,5(11)	0.011576393 1,750	A1,2B8,18DR3,7	0.002969437 6,800	A9,11B35,XDR1,2	0.00009807 205,000
A1,2B40,XDR4,5(11)	0.0014585252 13,500	A2,11B8,15DR3,X	0.001164998 17,500	A2,XB14,16DR2,3	0.000711052 29,000	A9(23),XB15,XDR5(11),X	0.000181608 112,000
A2,9(24)B27,35DR5(11),X	0.00349601 5,800	A2,11B18,XDR5(11),X	0.005669882 3,350	A2,31B15,16(38)DR2(15),5(11)	0.0000831 245,000	A2,10(26)B5,16(39)DR4,5(11)	0.000475861 43,000
A1,2B5,8DR2(15),5(11)	0.004277584 1,150	A2,3B16,XDR5(11),X	0.000899189 23,000	A2,9(24)B27,XDR1,X	0.004278409 4,800	A1,32B5,35DR1,10	0.00009143 220,000
A1,10(26)B7,35DR1,5(11)	0.000359683 57, 000	A1,10(26)B14,35DR1,7	0.000202016 100,000	A2,XB17,35DR7,X	0.005407788 3,800	A1,2B5,12(44)DR5,7	0.00039336 52,000
A1,3B7,8DR3,X	0.007299668 2,800	A10,33B14,41DR1,X	0.000177773 115,000	A9(24),10B5(51),16(38)DR4,X	0.000244633 83,000	A2,XB5,7DR2,6(13)	0.000925634 22,000
A1,3B13,35DR7,X	0.001807573 11, 200	A3,9(24)B15,40DR5(11),X	0.0002126 95,000	A2,9(24)B12(44),35DR4,X	0.000572269 35,000	A9(24),32B8,27DR3,6(13)	0.000022459 900,000
A1,28B8,35DR3,X	0.002200238 9,200	A2,11B12(44),XDR5(12),X	0.000308802 65,000	A9(24),XB7,17DR2,X	0.00066789 30,000	A2,10B12(44),16DR2,4	0.00016666 122,000
A2,XB5,XDR2,X	0.019198794 1,050	A9(24),XB14,XDR1,X	0.000980275 21,000	A30,XB7,12(44)DR5(11),X	0.000210323 96,000	A1,29B5,8DR3,4	0.000245823 82,000
A3,XB7,12(44)DR2,X	0.002463736 8,200	A2,3B7,8DR3,4	0.001173968 17,500	A2,XB17,XDR3,X	0.00334861 6,000	A1,2B17,35DR525(11)	0.000774699 26,000
A1,2B8,22DR2(15),3	0.00172105 12,000	A2,XB27,XDR5(11),X	0.029625518 670	A2,XB5(51),35DR5(11),X	0.006656406 3,000	A2,XB5,7DR2(15),6(13)	0.00925634 2,200
A1,10B8,16DR2,3	0.001654932 12,500	A3,9B22,XDR4,5(11)	0.000026314 770,000	A2,XB13,35DR5(11),7	0.000763507 27,000	A1,28B8,16(38)DR2(15),3	0.000173682 119,000
A1,2B5(51),8DR3,7	0.00185252 11,000	A3,XB14,27DR2,3	0.000065496 310,000	A2,XB18,XDR1,X	0.008367627 2,400	A2,10(26)B16(38),35DR5(11),8	0.000163634 125,000
A1,10B7,XDR2,3	0.000210349 97,000	A3,9(24)B7,18DR2(15),5(11)	0.001611697 12,500	A2,XB5,XDR6(13),X	0.004942416 4,100	A2,32B12(44),13DR2(16),6(13)	0.000006874 3 000,000
A1,11B8,35 DR1,2(15)	0.001172844 17,500	A1,3B8,XDR3,4	0,003981221 5,100	A1,2B35,XDR2,XD	0.009860422 2,050	A1,2B8,12(44)DR5(11),X	0.001450787 14,000
A2,11B5,14DR1,2	0.000277767 73,000	A1,10(25)B8,17DR7,X	0.0003900976 47,000	A10(25),XB18,XDR5(11),X	0.004009944 5,000	A1,10(26)B7,13DR8,X	0.000019713 1 050,000
A9(24),11B35,40DR1,X	0.00046574 43,000	A2,30B13,15DR7,X	0.000632496 32,000	A2,XB5,7DR2,X	0.004877957 4,200	A3,9B8,13DR6(13),7	0.000022981 900,000
A1,10(26)B35,XDR1,5(11)	0.001549033 13,000	A2,XB12(44),XDR3,X	0.00036216 56,000	A2,XB8,16(38)DR3,X	0.002683156 7,500	A2,11B17,35DR1,7	0.001066658 19,000
A9,10B14,22DR1,2	0.000046294 440,000	A2,9(24)B5(51),XDR5(11),8	0.000518401 39,000	A2,XB21,XDR2(15),X	0.003595805 5,700	A2,3B5,XDR6(14),X	0.000358099 57,000

pp – phenothypes of patients, op/nd – occurence probability, nd – number of neccesarry donors

(continued on the next page)

TABLE 3
PROBABILITY OF PHENOTYPE OCCURENCE AND NUMBER OF NECESSARY DONORS
(continued from the previous page)

pp	op/nd	pp	op/nd	pp	op/nd	pp	op/nd
A1,11B8,35DR3,5	0.000590621 35,000	A2,XB13,27DR1,7	0.000426752 47,000	A1,9(24)B18,XDR2,4	0.000694973 29,000	A1,XB5,8DR1,3	0.002969098 6,800
A2,9B21,40DR1,6(14)	0.000042855 470,000	A1,2B8,40DR2(15),3	0.001815392 11,300	A2,9(24)B5(51),XDR7,X	0.004192385 4,800	A2,9(24)B5,12(44)DR2(15),5(11)	0.000363102 57,000
A1,2B5,27DR2(15),5(11)	0.001403168 14,500	A3,XB5(51),15DR5(11),X	0.00037192 55,000	A1,2B5(51),18DR2,5(51)	0.001960917 10,500	A2,10(25)B5,15DR2,5(12)	0.000039481 520,000
A1,28B8,14DR2,5	0.000034565 580,000	A2,33B14,XDR1,X	0.005022998 4,000	A2,XB13,XDR2(15),7	0.002526472 8,000	A2,11B27,35DR2(15),6(13)	0.000157796 130,000
A3,9B7,12(44)DR2,X	0.000372172 55,000	A10,XB16,XDR4,5(11)	0.000742923 27,000	A2,9(24)B5(51),XDR6,X	0.001699587 12,000	A2,11B16,40DR1,2(15)	0.000132915 155,000
A1,10B8,16DR3,4	0.001487498 13,500	A9(24),XB16,17DR2(15),X	0.000085713 240,000	A2,XB21DR7,X	0.000578532 35,000	A1,2B8,12DR2,10	0.000277629 72,500
A11,33B14,27DR3(17),5(11)	0.000035086 580,000	A10(25),XB7,18DR2(15),X	0.000534765 38,000	A1,10B5,8DR2,3	0.000574952 35,000	A2,3B7,18DR2,5(11)	0.000748066 27,000
A3,10(26)B16(38),XDR2(150,4	0.000102935 200,000	A2,9B5(51),XDR3,X	0.000804464 25,000	A11,XB35,XDR2,X	0.002013901 10,000	A3,11B12(44),17DR1,7	0.000100177 200,000
A1,3B7,8DR3,4	0,00158385 13,000	A1,10B5(51),16(38)DR1,2	0.000076151 270,000	A10,XB18,XDR1,X	0.000701723 29,000	A2,10(26)B18,22DR5(11),8	0.000077687 260,000
A9(24),10(26)B5(51),XDR1,4	0.00034739 580,000	A1,XB8,17DR3,8	0.003259396 6,200	A1,XB35,XDR3,X	0.003282816 6,300	A1,2B16(38),37DR5(11),10	0.000095 215,000
A9(24),30B15,XDR4,8	0.000031964 630,000	A2,XB14,27DR4,5(12)	0.000065311 310,000	A1,XB5,XDR2,9	0.000480726 43,000	A2,3B14,XDR1,2	0.001513936 13,500
A1,3B8,21DR3,4	0.001006296 20,000	A11,XB18,XDR5(11),10	0.000349266 58,000	A1,9(24)B18,XDR3,5(11)	0.000179309 115,000	A2,9B5,7DR2(15),5	0.000334255 55,000
A2,X B18,27DR4,6(14)	0.0002551213 80,000	A3,32B5,7DR5(11),10	0.000112597 180,000	A2,XB5,12(44)DR2,X	0.003741893 5,500	A1,2B7,8DR2(15),3	0.004404231 4,600
A2,XB5,15DR6(13),X	0.00135241 15,000	A1,XB5,XDR2(15),X	0.006673702 3,000	A1,11B18,XDR2,X	0.002025401 10,000	A9(24),10B18,48DR3,4	0.000145128 140,000
A1,XB5(51),XDR2(15),X	0.001254092 16,000	A1,2B16,17DR2,7	0.000780651 26,000	A10,11B15,18DR5(11),X	0.000360804 56,000	A2,32B5,21DR5(11),X	0.000623445 33,000
A1,3B7,35DR1,2(15)	0.00118432 17,000	A1,9(24)B8,12(44)DR2(15),X	0.000357984 56,000	A1,33B14,37DR2,3	0.00013332 155,000	A1,XB40,XDR7,X	0.000670167 30,000
A2,9(24)B16,37DR2,10	0.000080204 250,000	A10(25),XB18,XDR2,X	0.001716298 12,000	A1,2B5,XDR2(15),5(11)	0.005324605 3,800	A9,XB21,27DR5(11),X	0.000470298 43,000
A9(24),11B12(44),27DR2,6(13)	0.000176841 116,000	A2,XB18,XDR1,X	0.007638119 3,000	A2,XB5,13DR4,7	0.001858618 11,000	A2,9(24)B27,XDR2,5(11)	0.003449256 5,900
A2,10B27,35DR5(11),X	0.00073319 25,000	A1,2B8,13DR3(18),7	0.000331899 62,000	A9(24),XB12(44),XDR5(11),X	0.003639787 5,500	A1,10(26)B21,XDR4,9	0.00043427 470,000
A1,2B5(51),XDR2,5(11)	0.013190071 1,550	A2,33B8,14DR1,3	0.001677153 12,000	A30,XB13,35DR2,X	0.000119693 170,000	A2,XB21,37DR1,X	0.000541603 37,000
A3,9(24)B13,35DR4,7	0.000081564 250,000	A2,3B14,35DR5(11),X	0.001010764 20,000	A2,XB18,XDR1,2(15)	0.003862264 5,300	A3,XB7,14DR10,X	0.00098671 20,500
A2,9(24)B27,XDR5(11),X	0.018815232 1,070	A2,XB5(51),16DR6(13),X	0.000591623 35,000	A1,XB17,35DR7,X	0.005046412 4,000	A2,3B18,21DR9,X	0.000278146 73,000
A2,3B5(51),40DR4,5(11)	0.000502498 40,000	A3,10B40,XDR4,X	0.000295785 68,000	A2,11B5(51),12(440DR2,X	0.001829689 11,000	A2,9B12,18DR1,5(11)	0.000557438 37,000
A1,11B35,40DR5(11),X	0.001505451 13,500	A9(24),XB5(51),7DR2(15),X	0.0006625 31,000	A10(26),32B16(38),XDR1,X	0.000379489 53,000	A1,2B5(51),8DR3,5(11)	0.008780306 2,300
A1,2B27,35DR5(11),X	0.00569633 3,600	A2,XB18,XDR2(15),X	0.003731527 5,500	A3,9(24)B8,18DR3,4	0.000464768 44,000	A3,11B17,18DR7,8	0.00005161 400,000

pp – phenothypes of patients, op/nd – occurence probability, nd – number of neccesarry donors

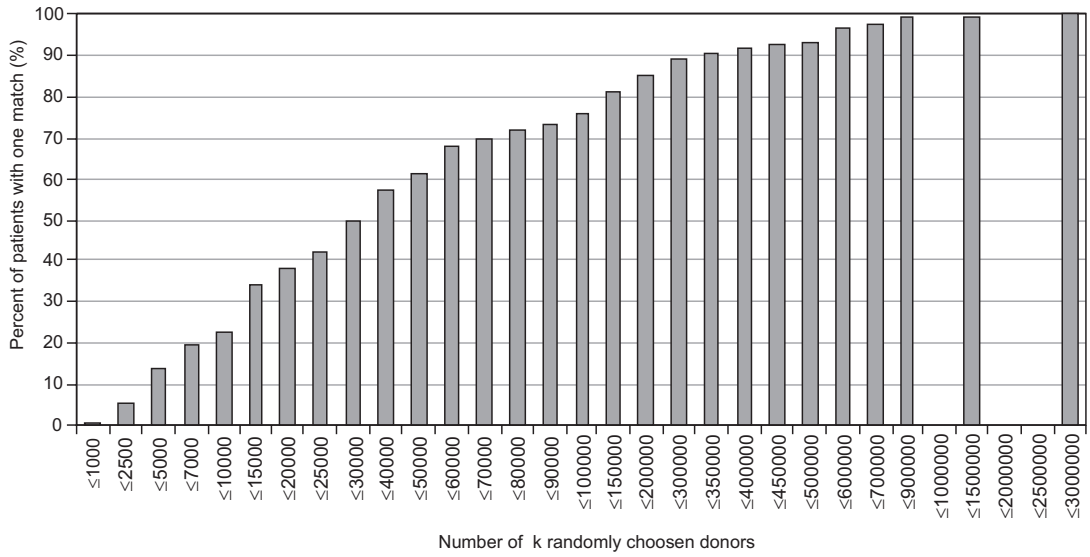

Fig. 1. Percentage of patients who have at least one HLA identical unrelated donor with 99.99% probability among k randomly choosen donors. k-randomly choosen donor.

cent of patients. The population of patients was tested for fit to Hardy-Weinberg equilibrium (HWE), for each locus, using a chi-squared goodness-of-fit test.

Results

Table 1 presents the phenotype frequencies of HLA A, B and DR antigens in the population of Vojvodina.

Table 2 presents the observed AB and BDR haplotype frequencies.

The most frequent AB haplotypes are A1B8 (0.155), A2B5(0.105), A2B35(0.065) while the most frequent BDR haplotypes are: B8DR3(0.135), B35DR5(11) (0.06) and B8DR2(15)(0.045).

Table 3 shows the probabilities that 200 patients from Vojvodina would have a given HLA phenotype. The relation between the probabilities of finding a match for 200 patients and registry size is also presented in Table 3. The probability that a random patient will have a given phenotype is in inverse proportion to the necessary donors (k randomly choosen donors), that achieve a match with 99.99%: the lower probability of occurence of certain HLA phenotype, the higher the number of k randomly choosen donors for finding at least one HLA identical donor in a registry. Figure 1 shows the percentages of patients who would theoretically be able to have at least one matched donor among k randomly chosen donors. There was a good fit to Hardy-Weinberg equilibrium and the proportion of homozygotes was as expected (^{2} test for A locus = 0.156, for B locus = 1.167, for DR locus = 1.664, border value 3.841).

Discussion

The chance of finding unrelated bone marrow donor depends on the frequency of the patient's HLA phenotype, degree of histoincompatibility considered acceptance and the size of the donor registry[2,3,6,12]. It is expected that individuals with HLA phenotypes of higher frequencies will have a higher probability of finding a matched donor[25,26]. Furthermore, identification of the donors who inherit common HLA haplotypes in significant gametic disequilibrium provide the higher rates of successfull unrelated donor searches[5,7,27–29]. Our results showed the proportional influence of HLA phenotype frequency on the probability of finding at least one match among k randomly chosen donors. It is noticable from the example where the patients with the most common haplotypes, with similar frequency in many other Caucasoid European populations[30–37], such as A2B5DR2 and A1B8DR3, especially ones with homozygosity or undetected alleles at a loci, require smaller donor size in comparison to the others (Table 3). Great determinant of the probability of matching and consequent registry size requirements is frequency of genotypes with blank or homozygous alleles. They express the direct influence to the number of k randomly choosen donors: the higher frequency of blank alleles, the lower number of k randomly choosen donors. From our results it is noticable that probability of finding HLA identical unrelated donor is in inverse proportion with the number of k randomly choosen unrelated donors necessary for research with an aim to find at least one HLA identical donor. Lower probability of finding HLA identical donor is appropriate to a higher number of donors necessary for research as well as to bigger request of the registry pool size. From the number of potential donors required for various probabilities, we estimated the percentages of patients who find at least one HLA identical unrelated donor (Figure 1). According to the results of a registry model, for more than 45% of the patients from Vojvodina (99 patients or 49.5%), required pool size of the registry is 30,000 donors. Remaining 50.5% of patients, require a bigger donor file, which show

that effectiveness of a regional bone marrow donor registry in Vojvodina gradually decreases. Also our results show relatively high effectiveness, because in the registry with 40.000 donors, 57% of patients can find HLA identical donor or 42.5% of patients can locate HLA phenotypically identical donor in the registry with less than 25,000 donors (Figure 1). Our results about a regional bone marrow registry effectiveness, show the specific success rate of identifying a HLA A,B and DR matched donors that is distinctive for Vojvodina. There are the differences in effectiveness of various regional bone marrow registries that are understandable in terms of genetic variation in distinct racial or ethnic groups with typical distribution of HLA genotypes. For example, the French registry composed of 70,000 donors, provided at least one match for only 20% Caucasoid patients. In the contrast, the Hong Kong registry of 17,000 donors provided a 42% success rate of identifying HLA A,B and DR matched donors[4]. To enable more than 80 percent of patients to have at least one HLA identical donor, only 50,000 potential donors would be necessary for Japanese persons, whereas 1 000,000, 400,000 and 25,000, respectively, would be required for European, North American Whites and Western Indians[4,6]. This study shows that regional registry could locate unrelated donors for a great number of patients from Vojvodina. However, an expanded number of donors would be necessary to allow an extensive evaluation of unrelated marrow transplantation, since the local transplant centers in Vojvodina would accept to perform transplantation with hematopoietic stem cells from unrelated HLA identical donors or donors mismatched only for HLA antigens belonging to same crossreactive group.

Conclusion

This study shows that the method described here could be used to estimate donor pool size requirements using any population for which HLA haplotype and phenotype frequencies are available. To enable more than 45 percent of patients from Vojvodina to have at least one HLA A,B and DR identical donor, 30,000 potential donors would be necessary. These findings support the idea of justifiableness for establishing the regional bone marrow registry in Vojvodina.

Acknowledgements

The technical assistance of Ivana Bogdanović-Mudrinski is gratefully appreciated. The authors thank Jasna Skomrak for her assistance with the statistical analysis of data. Staf members of HLA laboratory in the Departement of immunoserological and immunogenetical investogations are cordially thanked for providing data used in this paper.

REFERENCES

1. POPOVIĆ S, Bone Marrow transplantation in acute nonlymphoblastic leukaemia-ethical risks and optimal time (Prometej, Novi Sad, 1996). — 2. VOJVODIĆ S, HLA system and allogeneic stem cell transplantation in leukaemias and myelodysplastic syndrome, PhD Thesis (University of Novi Sad, Novi Sad, 2003). — 3. MCCOLLOUGH J, SCOTT EP, HALAGAN N, STRAND RA, MC GLAVE P, J Am Med Assoc, 22 (1988) 3286. — 4. GHOSH K, SHANKARKUMAR U, MOHANTY D, Transfus Med 12 (2002) 43. — 5. ANSART-PIRENNE H, DUFOSSE F, DUVAL M, CRACCO P, JAMBOU M, PERDON B, VILMER BE, STERKES G, Tissue Antigens 57 (2001) 163. — 6. TAKAHASHI K, JUJI T, MIYAZAKI H, Transfusion 4 (1989) 311. — 7. O'REILLY RJ, BROCHSTEIN J, COLLONS N, KEEVER C, KAPOOR N, KIRKPATRICK D, KERNAN N, DUPONT B, BURNS J, REISNER Y, Vox Sang 51 (1986) 81. — 8. BEATTY PG, CLIFT RA, MICKELSON EM, NISPEROS BB, FLOURNOY N, MARTIN PJ, SANDERS JS, STEWART P, BUCKNER D, STORB R, THOMAS ED, N Engl J Med, 13 (1985) 765. — 9. BASARA N, Unrelated donor hematopoetic stem cell transplantation. In: MILENKOVIĆ P (Eds), Novelties in hematology II (Udruženje hematologa Jugoslavije, Beograd, 2000). — 10. MCGLAVE PB, SHU XO, WEN W, ANASETTI C, NADEMANEE A, CHAMPLIN R, ANTIN JH, KERNAN NA, KING R, WEISDORF DJ, Blood, 7 (2000) 2219. — 11. WEISDORF DJ, ANNASETTI C, ANTIN JH, KERNAN NA, KOLLMAN C, SNYDER D, PETERSDORF E, NELSON G, MC GLAVE P, Blood, 6 (2002) 1971. — 12. SPEISER DE, TIERCY J-M, RUFER N, GRUNDSCHOBER C, GRATWOHL A, CHAPUIS B, HELG C, LOLIGER CC, SIREN MK, ROOSNEK E, JEANENET M, Blood, 10 (1996) 4455. — 13. MORISHIMA Y, SASAZUKI T, INOKO H, JUJI T, AKAZA T, YAMAMOTO K, ISCHIKAWA Y, KOTO S, SAO H, SAKAMAKI H, KAWA K, HAMAJIMA N, ASANO S, KODERA Y, Blood, 11 (2002) 4200. — 14. SCHIPPER RF, OUDSHOORN M, D'AMARO J, VAN DER ZADEN HGM, DE LANGE P, BAKKER JT, BAKKER J, VAN ROOD JJ, Tissue Antigens, 47 (1996) 169. — 15. The Anthony Nolan Trust-where leukaemia meets its match, Available from: http:// www.anthonynolan.org.uk/ndonors/patients.html, accessed: September 10, 2002. — 16. SONNENBERG FA, ECKMAN MH, PAUKER SG, Blood 7 (1989)2569. — 17. RUUTU T, GOLDMAN JM, Bone Marrow Transplant 5(1990)237. — 18. KERNAN NA, BARTSCH G, ASH RC, BEATTY PG, RICHARD C, FILIPOVICH A, GAJEWSKI J, HANSEN JA, HANSLE-DOWNEY J, MC CULLOUGH J, MC GLAVE P, PERKINS HA, PHILLIPS GL, SANDERS J, STRONCEK D, THOMAS ED, BLUME KG, N Engl J Med, 9 (1993) 593. — 19. Bone Marrow Donors Worldwide, Available from: http ://www. bmdw.org, accessed: September 10, 2002. — 20. STRONCEK D, BARTSCH G, PERKINS HA, RANDALL BL, HANSEN JA, MC CULLOUGH J, Transfusion 7 (1993) 567. — 21. STOLIĆ I, PAUNOVIĆ D, SIMONOVIĆ R, MILETIĆ VD, Bilt hematol transfuz. 19 (1991) 42. — 22. ZERGOLLERN LJ, Humana genetika (Jugoslovenska medicinska naklada, Zagreb, 1991). — 23. NIJENHUIS LE, D'AMARO J, Tissue Antigens 26 (1985) 215. — 24. SCHIPPER RF, D'AMARO J, OUDSHOORN M, The probability of finding a haplotypically identical unrelated bone marrow donor. In: DOMINIQUE C (Eds), Genetic diversity of HLA functional and medical implication (EDK, Medical and scientific international publisher, Paris, 1997). — 25. SHAW CK, CHANG TK, CHEN SN, WU S, Tissue Antigens, 6 (1997) 610. — 26. SCHIPPER RF, D'AMARO J, BAKKER JT, BAKKER J, VAN ROOD JJ, OUDSHOORN M, Hum Immunol, 52 (1997) 54. — 27. OUDSHOORN M, CORNELISSEN JJ, FIBBE WE, DE GRAFF-MEEDER ER, LIE JLWT, SCHREUDER T, SINTNICOLAAS K, WILLEMZE R, VOSSEN JMJJ, VAN ROOD JJ, Bone Marrow Transplant, 20 (1997) 1011. — 28. PERDON B, DUVAL M, ELBOU OM, MOSKWA M, JAMBOU M, VILMER E, STERKERS G, Bone Marrow Transplant, 31 (2003) 423. — 29. VIDAN-JERAS B, BREURVRIESENDORP B, BOHINJEC M, JEANNET M, ROOSNEK E, TIERCY J-M, Eur J Immunogenet, 24 (1997) 335. — 30. CRNIĆ- MARTINOVIĆ M, VUJAKLIJA-STIPANOVIĆ K, RISTIĆ S, FUĆAK M, KAPOVIĆ M, WEINER M, SEPČIĆ J, Coll Antropol, 26 (2002) 69. — 31. IVANOVA M, SPASSOVA P, MICHAILOVA A, NAUMOVA E, Tissue Antigens, 57 (2001) 208. — 32. HILLER C, BISCHOFF M, SCHMIDT A, BENDER K, Hum Genet, 41 (1978) 301. — 33. RENIERI N, STAVROPULOS C, LEPAGE V, Tissue Antigens, 13 (1979) 154. — 34. CARVALHO AS, Tissue Antigens, 21 (1983) 39. — 35. YOUINOU P, GUEGUEN A, HALLE L, JOUQUAN J, SALMON D, MENN GL, RUFFIE J, SALMON C, Tissue Antigens, 22 (1983) 348. — 36. JAZWINSKA EC, KILPATRICK DC, Tissue Antigens, 29 (1987) 115. — 37. ZAPPACOSTA S, FELICE MD, FIORE M, FERRARA GB, Tissue Antigens, 16 (1980) 286.

S. Vojvodić

Institute for blood transfusion Novi Sad, Hajduk Veljkova 9a, 21 000 Novi Sad, Serbia
e-mail: ssvu@eunet.yu

PREDIKTIVNI PRORAČUN EFEKTIVNOSTI REGIONALNOG REGISTRA DONORA KOSTNE SRŽI U VOJVODINI

S A Ž E T A K

Cilj ove studije je određivenje postotka bolesnika sa područja Vojvodine, koji bi našli bar jednog HLA identičnog nesrodnog donora u registru sa različitim brojem donora. Radi određivanja vjerovatnoće da će 200 bolesnika posjedovati određeni fenotip, izračunavane su haplotipske frekvencije za tri lokusa HLA sistema, putem definiranja frekvencija HLA A, B i DR antigena kao i uočenih frekvencija AB i BDR haplotipova. Nakon toga izračunavani su postoci bolesnika koji teoretski posjeduju barem jednog HLA identičnog nesrodnog donora u registru sa određenim brojem donora. Prema rezultatima uzorka iz studije, prediktivna procjena efektivnosti regionalnog registra donora koštne srži u Vojvodini bi bila 14% sa 5,000 donora, 23% sa 10,000 donora, 38.5% sa 20,000 donora, 49.5% sa 30,000 donora i 76% sa 100,000 donora u registru. Broj donora u registru koji bi osigurao nalaženje bar jednog HLA identičnog donora za više od 45% bolesnika područja Vojvodine je 30,000 donora.