

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

Svetlana Vojvodić¹ and Stevan L. Popović²

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/HSCT¹⁻⁶. 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 at least five of six HLA-A,B and -DR antigens⁹⁻¹³. 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.

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 syndrome²¹. 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 allele²². 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 frequencies²³.

The frequency of the phenotype $P(A_1A_2B_1B_2DR_1DR_2)$ was calculated by following formula: $P_1 = \frac{\sum Q(A_1B_1DR_1) \times Q(A_2B_2DR_2)}{\text{all possible combinations}}$, where the summation is divided by all possible combinations of the haplotypes that yield the phe-

notype under consideration⁶. In the case of homozygosity at a locus, procedure takes into account extra haplotypes that have an undetected antigen on these loci²⁴. 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 phenotype¹⁶. 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 appropriate number of k randomly chosen donors, was gradually increased with an aim to achieve 99.99% probability of finding compatible donor that is in accordance with the HLA phenotypic frequencies of the recipients. 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		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		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 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	/	0.005	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	0.005	0.005	0.015	0.01	0.01	0.01	0.01	0.02	0.02	0.005	0.015	0.015	0.015	0.015	0.005	0.005	/	0.005	0.05
DR5	0.01	0.005	/	0.005	0.01	0.005	/	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	/	0.005	/	/	/	0.015	0.01	/	/	0.005	/	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	0.06	/	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 OCCURRENCE AND NUMBER OF NECESSARY DONORS

pp	op/nd	pp	op/nd	pp	op/nd	pp	op/nd	pp	op/nd
A2,XB35,XDR5,7	0.000144199	A1,2B5(51),8DR3,5(11)	0.007664117	A2,30B14,21DR4,X	0.000114281	A2,10(25)B5(51),27DR1,7	0.000051416		
	140,000		2,650		180,000		400,000		
A1,33B17,35DR1,6(13)	0.000035396	A2,30B5(51),35DR4,X	0.000276879	A1,2B5,12(44)DR1,X	0.000721549	A9(24),XB12(44),18DR5(11),7	0.000762739		
	570,000		73,000		28,000		2,000		
A2,XB18,41DR5(11),X	0.001905322	A1,9(24)B8,18DR5(11),X	0.00271723	A2,XB21,XDR5(11),X	0.006160568	A1,2B5(51),21DR4,6	0.000208491		
	10,800		7,500		3,300		97,000		
A2,10(26)B16(38),47DR6(13),X	0.00035	A11,XB21,22DR2(15),3	0.000039282	A2,9(24)B5(51),17DR3,7	0.000757141	A2,XB5(51),XDR2,5	0.009548307		
	58,000		520,000		27,000		2,100		
A2,XB12(44),16(39)DR4,5(11)	0.00031625	A28,32B5(51),7DR1,X	0.00002642	A3,XB18,35DR1,2	0.000624982	A2,9(24)B5,41DR4,7	0.000100572		
	65,000		780,000		33,000		200,000		
A2,33B12(45),14DR1,X	0.000611097	A28,10(26)B51,52DR2,4	0.000053844	A2,28B5,16DR2,X	0.0004306	A2,10(25)B18,21DR2,3	0.000222233		
	33,000		380,000		47,000		92,000		
A2,XB22,27DR2,5(11)	0.001135963	A1,XB8,18DR3,5(11)	0.011576393	A1,2B8,18DR3,7	0.002969437	A9,11B35,XDR1,2	0.00009807		
	18,000		1,750		6,800		205,000		
A1,2B40,XDR4,5(11)	0.0014585252	A2,11B8,15DR3,X	0.001164998	A2,XB14,16DR2,3	0.000711052	A9(23),XB15,XDR5(11),X	0.000181608		
	13,500		17,500		29,000		112,000		
A2,9(24)B27,35DR5(11),X	0.00349601	A2,11B18,XDR5(11),X	0.005669882	A2,31B15,16(38)DR2(15),5(11)	0.0000831	A2,10(26)B5,16(39)DR4,5(11)	0.000475861		
	5,800		3,350		245,000		43,000		
A1,2B5,8DR2(15),5(11)	0.004277584	A2,3B16,XDR5(11),X	0.000899189	A2,9(24)B27,XDR1,X	0.004278409	A1,32B5,35DR1,10	0.00009143		
	1,150		23,000		4,800		220,000		
A1,10(26)B7,35DR1,5(11)	0.000359683	A1,10(26)B14,35DR1,7	0.000202016	A2,XB17,35DR7,X	0.005407788	A1,2B5,12(44)DR5,7	0.00039336		
	57,000		100,000		3,800		52,000		
A1,3B7,8DR3,X	0.007299668	A10,33B14,41DR1,X	0.000177773	A9(24),10B5(51),16(38)DR4,X	0.000244633	A2,XB5,7DR2,6(13)	0.000925634		
	2,800		115,000		83,000		22,000		
A1,3B13,35DR7,X	0.001807573	A3,9(24)B15,40DR5(11),X	0.0002126	A2,9(24)B12(44),35DR4,X	0.000572269	A9(24),32B8,27DR3,6(13)	0.000022459		
	11,200		95,000		35,000		900,000		
A1,28B8,35DR3,X	0.002200238	A2,11B12(44),XDR5(12),X	0.000308802	A9(24),XB7,17DR2,X	0.00066789	A2,10B12(44),16DR2,4	0.00016666		
	9,200		65,000		30,000		122,000		
A2,XB5,XDR2,X	0.019198794	A9(24),XB14,XDR1,X	0.000980275	A30,XB7,12(44)DR5(11),X	0.000210323	A1,29B5,8DR3,4	0.000245823		
	1,050		21,000		96,000		82,000		
A3,XB7,12(44)DR2,X	0.002463736	A2,3B7,8DR3,4	0.001173968	A2,XB17,XDR3,X	0.00334861	A1,2B17,35DR525(11)	0.000774699		
	8,200		17,500		6,000		26,000		
A1,2B8,22DR2(15),3	0.00172105	A2,XB27,XDR5(11),X	0.029625518	A2,XB5(51),35DR5(11),X	0.006656406	A2,XB5,7DR2(15),6(13)	0.00925634		
	12,000		670		3,000		2,200		
A1,10B8,16DR2,3	0.001654932	A3,9B22,XDR4,5(11)	0.000026314	A2,XB13,35DR5(11),7	0.000763507	A1,28B8,16(38)DR2(15),3	0.000173682		
	12,500		770,000		27,000		119,000		
A1,2B5(51),8DR3,7	0.00185252	A3,XB14,27DR2,3	0.000065496	A2,XB18,XDR1,X	0.008367627	A2,10(26)B16(38),35DR5(11),8	0.000163634		
	11,000		310,000		2,400		125,000		
A1,10B7,XDR2,3	0.000210349	A3,9(24)B7,18DR2(15),5(11)	0.001611697	A2,XB5,XDR6(13),X	0.004942416	A2,32B12(44),13DR2(16),6(13)	0.000006874		
	97,000		12,500		4,100		3,000,000		
A1,11B8,35 DR1,2(15)	0.001172844	A1,3B8,XDR3,4	0.003981221	A1,2B35,XDR2,XD	0.009860422	A1,2B8,12(44)DR5(11),X	0.001450787		
	0.000277767		5,100		2,050		14,000		
A2,11B5,14DR1,2	0.000277767	A1,10(25)B8,17DR7,X	0.0003900976	A10(25),XB18,XDR5(11),X	0.004009944	A1,10(26)B7,13DR8,X	0.000019713		
	73,000		47,000		5,000		1,050,000		
A9(24),11B35,40DR1,X	0.00046574	A2,30B13,15DR7,X	0.000632496	A2,XB5,7DR2,X	0.004877957	A3,9B8,13DR6(13),7	0.000022981		
	43,000		32,000		4,200		900,000		
A1,10(26)B35,XDR1,5(11)	0.001549033	A2,XB12(44),XDR3,X	0.00036216	A2,XB8,16(38)DR3,X	0.002683156	A2,11B17,35DR1,7	0.001066658		
	13,000		56,000		7,500		19,000		
A9,10B14,22DR1,2	0.000046294	A2,9(24)B5(51),XDR5(11),8	0.000518401	A2,XB21,XDR2(15),X	0.003595805	A2,3B5,XDR6(14),X	0.000358099		
	440,000		39,000		5,700		57,000		

pp – phenotypes of patients, op/nd – occurrence probability, nd – number of necessary donors

(continued on the next page)

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

pp	op/nd	pp	op/nd	pp	op/nd	pp	op/nd	pp	op/nd	pp	op/nd
A1,11B8,35DR3,5	0.000590621	A2,XB13,27DR1,7	0.000426752	A1,9(24)B18,XDR2,4	0.000694973	A1,XB5,8DR1,3	0.002969098				
A2,9B21,40DR1,6(14)	35,000	A1,2B8,40DR2(15),3	47,000	A2,9(24)B5(51),XDR7,X	29,000	A2,9(24)B5,12(44)DR2(15),5(11)	6,800				
A1,2B5,27DR2(15),5(11)	0.000042855	A3,XB5(51),15DR5(11),X	11,300	A1,2B5(51),18DR2,5(51)	0.004192385	A2,10(25)B5,15DR2,5(12)	0.000363102				
A1,2B8,14DR2,5	470,000	A2,33B14,XDR1,X	55,000	A2,XB13,XDR2(15),7	4,800	A2,11B27,35DR2(15),6(13)	57,000				
A3,9B7,12(44)DR2,X	0.001403168	A10,XB16,XDR4,5(11)	0.00037192	A2,9(24)B5(51),XDR6,X	0.001960917	A2,11B16,40DR1,2(15)	0.00039481				
A1,10B8,16DR3,4	14,500	A9(24),XB16,17DR2(15),X	5,000	A1,10B5,8DR2,3	10,500	A1,2B8,12DR2,10	520,000				
A11,33B14,27DR3(17),5(11)	0.00034565	A10(25),XB7,18DR2(15),X	4,000	A11,XB35,XDR2,X	0.002526472	A3,11B12(44),17DR1,7	0.000157796				
A3,10(26)B16(38),XDR2(15),4	0.000372172	A1,10B5(51),16(38)DR1,2	27,000	A10,XB18,XDR1,X	8,000	A2,10(26)B18,22DR5(11),8	0.000132915				
A1,3B7,8DR3,4	55,000	A1,XB8,17DR3,8	0.00085713	A1,XB35,XDR3,X	12,000	A1,2B16(38),37DR5(11),10	155,000				
A11,33B14,27DR3(17),5(11)	0.001487498	A2,XB14,27DR4,5(12)	240,000	A1,XB5,XDR2,9	0.000578532	A2,3B14,XDR1,2	0.000277629				
A3,10(26)B16(38),XDR2(15),4	13,500	A11,XB18,XDR5(11),10	38,000	A1,9(24)B18,XDR3,5(11)	35,000	A2,3B7,18DR2,5(11)	72,500				
A1,3B8,21DR3,4	0.00035086	A3,32B5,7DR5(11),10	0.000534765	A2,XB5,12(44)DR2,X	0.000574952	A2,10(26)B18,22DR5(11),8	0.000748066				
A1,3B7,8DR3,4	0.000102935	A1,XB5,XDR2(15),X	0.000804464	A10,XB18,XDR1,X	35,000	A1,2B16(38),37DR5(11),10	0.000100177				
A9(24),10(26)B5(51),XDR1,4	200,000	A1,10B5(51),16(38)DR1,2	25,000	A1,XB35,XDR3,X	0.002013901	A2,3B14,XDR1,2	0.000132915				
A9(24),30B15,XDR4,8	0.00158385	A1,XB8,17DR3,8	0.000076151	A1,10B5,8DR2,3	10,000	A2,3B7,18DR2,5(11)	155,000				
A1,3B8,21DR3,4	13,000	A2,XB14,27DR4,5(12)	270,000	A11,XB35,XDR2,X	29,000	A2,10(26)B18,22DR5(11),8	0.000277629				
A2,X B18,27DR4,6(14)	0.00034739	A1,XB5,XDR2(15),X	6,200	A10(26),32B16(38),XDR1,X	0.003259396	A1,2B16(38),37DR5(11),10	0.000748066				
A1,3B8,21DR3,4	580,000	A2,XB14,27DR4,5(12)	0.000065311	A1,XB5,XDR2,9	6,300	A2,3B14,XDR1,2	27,000				
A2,X B18,27DR4,6(14)	0.000031964	A11,XB18,XDR5(11),10	310,000	A1,9(24)B18,XDR3,5(11)	0.000480726	A2,3B7,18DR2,5(11)	215,000				
A1,3B7,8DR3,4	630,000	A3,32B5,7DR5(11),10	0.000349266	A2,XB5,12(44)DR2,X	43,000	A2,10(26)B18,22DR5(11),8	0.001513936				
A2,X B18,27DR4,6(14)	0.001006296	A1,XB5,XDR2(15),X	58,000	A10,XB18,XDR1,X	0.00179309	A1,2B16(38),37DR5(11),10	13,500				
A1,3B8,21DR3,4	20,000	A1,10B5(51),16(38)DR1,2	0.000112597	A1,XB35,XDR3,X	115,000	A2,3B14,XDR1,2	0.000334255				
A2,X B18,27DR4,6(14)	80,000	A2,XB14,27DR4,5(12)	180,000	A10(26),32B16(38),XDR1,X	5,500	A2,3B7,18DR2,5(11)	55,000				
A1,3B7,8DR3,4	0.002551213	A1,XB5,XDR2(15),X	0.006673702	A1,11B18,XDR2,X	0.000741893	A2,10(26)B18,22DR5(11),8	0.004404231				
A2,X B18,27DR4,6(14)	0.00135241	A1,2B16(38),37DR5(11),10	3,000	A10,11B15,18DR5(11),X	10,000	A1,2B16(38),37DR5(11),10	4,600				
A1,3B8,21DR3,4	15,000	A2,XB14,27DR4,5(12)	0.000780651	A1,33B14,37DR2,3	0.002025401	A2,3B14,XDR1,2	0.000145128				
A2,X B18,27DR4,6(14)	0.001254092	A1,2B16(38),37DR5(11),10	26,000	A10,11B15,18DR5(11),X	56,000	A2,3B7,18DR2,5(11)	140,000				
A1,3B7,8DR3,4	0.00118432	A1,9(24)B8,12(44)DR2(15),X	56,000	A1,33B14,37DR2,3	0.000360804	A2,3B14,XDR1,2	0.000623445				
A2,X B18,27DR4,6(14)	0.000080204	A10(25),XB18,XDR2,X	0.001716298	A1,2B5,XDR2(15),5(11)	155,000	A1,XB40,XDR7,X	33,000				
A1,3B7,8DR3,4	250,000	A2,XB18,XDR1,X	12,000	A2,XB5,13DR4,7	0.005324605	A9,XB21,27DR5(11),X	0.000670167				
A2,9(24)B16,37DR2,10	0.000176841	A2,XB18,XDR1,X	3,000	A1,2B5,XDR2(15),5(11)	3,800	A9,XB21,27DR5(11),X	30,000				
A9(24),11B12(44),27DR2,6(13)	116,000	A1,2B8,13DR3(18),7	0.000331899	A9(24),XB12(44),XDR5(11),X	11,000	A2,9(24)B27,XDR2,5(11)	0.000449256				
A2,10B27,35DR5(11),X	0.00073319	A2,33B8,14DR1,3	62,000	A9(24),XB12(44),XDR5(11),X	0.003639787	A1,10(26)B21,XDR4,9	0.00043427				
A1,2B5(51),XDR2,5(11)	25,000	A2,33B8,14DR1,3	0.001677153	A30,XB13,35DR2,X	5,500	A2,XB21,37DR1,X	470,000				
A3,9(24)B13,35DR4,7	0.013190071	A2,3B14,35DR5(11),X	12,000	A2,XB18,XDR1,2(15)	0.000119693	A2,XB21,37DR1,X	0.000541603				
A2,9(24)B27,XDR5(11),X	1,550	A2,XB5(51),16DR6(13),X	0.001010764	A1,XB17,35DR7,X	170,000	A3,XB7,14DR10,X	37,000				
A2,3B5(51),40DR4,5(11)	0.000081564	A3,10B40,XDR4,X	20,000	A1,11B5(51),12(44)DR2,X	0.003862264	A2,3B18,21DR9,X	0.00098671				
A1,11B35,40DR5(11),X	0.018815232	A2,XB5(51),16DR6(13),X	0.000591623	A2,11B5(51),12(44)DR2,X	5,300	A2,3B18,21DR9,X	20,500				
A1,2B27,35DR5(11),X	1,070	A3,10B40,XDR4,X	35,000	A2,11B5(51),12(44)DR2,X	4,000	A2,3B18,21DR9,X	0.000278146				
A1,11B35,40DR5(11),X	0.000502498	A9(24),XB5(51),7DR2(15),X	0.000295785	A10(26),32B16(38),XDR1,X	0.001829689	A2,9B12,18DR1,5(11)	73,000				
A1,2B27,35DR5(11),X	40,000	A2,XB18,XDR2(15),X	68,000	A10(26),32B16(38),XDR1,X	11,000	A1,2B5(51),8DR3,5(11)	0.000557438				
A1,2B27,35DR5(11),X	0.001505451	A2,XB18,XDR2(15),X	0.0006625	A3,9(24)B8,18DR3,4	53,000	A1,2B5(51),8DR3,5(11)	37,000				
A1,2B27,35DR5(11),X	13,500	A2,XB18,XDR2(15),X	31,000	A3,9(24)B8,18DR3,4	0.003731527	A1,2B5(51),8DR3,5(11)	0.008780306				
A1,2B27,35DR5(11),X	0.00569633	A2,XB18,XDR2(15),X	0.003731527	A3,9(24)B8,18DR3,4	0.000464768	A1,2B5(51),8DR3,5(11)	2,300				
A1,2B27,35DR5(11),X	3,600	A2,XB18,XDR2(15),X	5,500	A3,9(24)B8,18DR3,4	44,000	A1,2B5(51),8DR3,5(11)	0.00050161				
							400,000				

pp – phenotypes of patients, op/nd – occurrence probability, nd – number of necessary donors

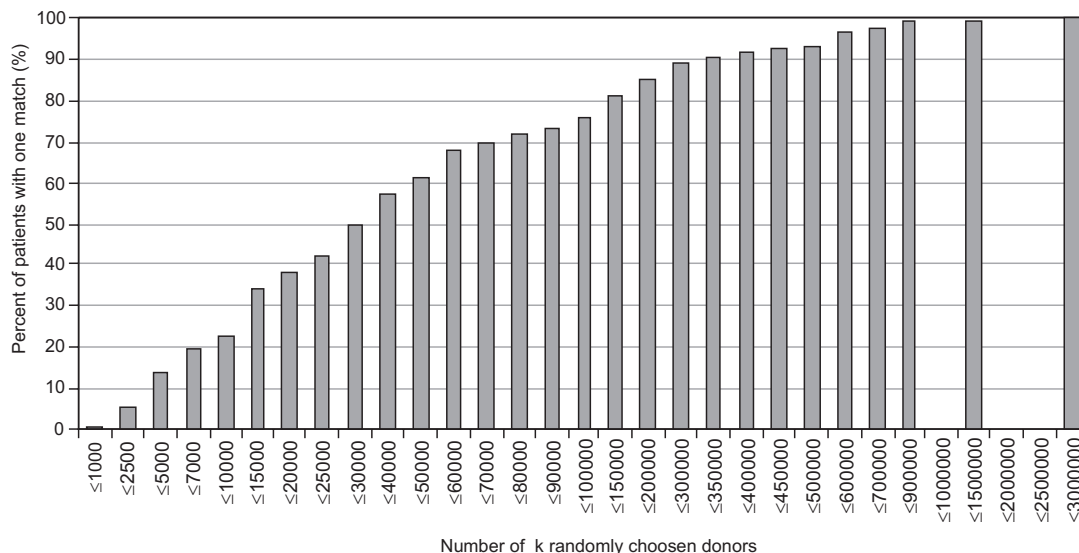


Fig. 1. Percentage of patients who have at least one HLA identical unrelated donor with 99.99% probability among k randomly chosen donors. k-randomly chosen donor.

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 chosen donors), that achieve a match with 99.99%: the lower probability of occurrence of certain HLA phenotype, the higher the number of k randomly chosen 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 (χ^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 pheno-

type, 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 successful 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 noticeable from the example where the patients with the most common haplotypes, with similar frequency in many other Caucasoid European populations³⁰⁻³⁷, 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 chosen donors: the higher frequency of blank alleles, the lower number of k randomly chosen donors. From our results it is noticeable that probability of finding HLA identical unrelated donor is in inverse proportion with the number of k randomly chosen 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 donors⁴. 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 transplanta-

tion, 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-Murdrinski 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 investigations 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, DUFOSSÉ 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 hematopoietic stem cell transplantation. In: MILENKOVIC P (Eds), Novelities in hematology II (Udruženje hematologa Jugoslavije, Beograd, 2000). — 10. MCGLAIVE 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, ANASETTI 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, HANSLÉ-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, SIMONOVIC R, MILETIĆ VD, Bilt hematol transfuz. 19 (1991) 42. — 22. ZERGOLLEARN LJ, Humana genetika (Jugoslavenska 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, CORNELISSSEN JJ, FIBBE WE, DE GRAFF-MEEDER ER, LIE JLWT, SCHREUDER T, SINTNICOLAAS K, WILLEMZE R, VOSSSEN JMJJ, VAN ROOD JJ, Bone Marrow Transplant, 20 (1997) 1011. — 28. PERDON B, DUVAL M, ELBOU OM, MOSKWA M, JAMBOU M, VILMER E, STERKES 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, VUJAKLJA-STIPANOVIĆ K, RISTIĆ S, FUČAK M, KAPOVIĆ M, WEINER M, SEPIĆIĆ 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, LE-PAGE V, Tissue Antigens, 13 (1979) 154. — 34. CARVALHO AS, Tissue Antigens, 21 (1983) 39. — 35. YOUINOUP 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 odredivenje 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.