Multiple myeloma

Incidence of monoclonal B-cell disease in siblings of patients with multiple myeloma

We observed clustering of monoclonal B-cell disease in siblings being screened as allogeneic donors for patients with multiple myeloma (MM) scheduled for stem cell transplantation (SCT). Of 134 asymptomatic donors, the incidence of monoclonal B-cell disease was 8/84 in siblings and 1/50 in matched unrelated donors. From an analysis of five MM families scheduled for allogeneic SCT, monoclonal B-cell disease was detected in 8/27 siblings.

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High-dose chemotherapy with autologous stem cell transplantation (SCT) has been demonstrated to be beneficial for patients with multiple myeloma (MM). However, for patients with advanced disease and adverse prognostic factors, a strategy of autologous SCT, followed by an allogeneic transplant is being evaluated is trials. Since allogeneic SCT has been shown to be potentially curative for MM patients, this approach is being used more frequently and with increasing success also in older patients. Between 1/1992 and 6/2004, 38 MM patients underwent allogeneic SCT at our institution. Due to the accidental detection of a monoclonal B-cell disease in one MM family in 1999, we evaluated all siblings of MM patients before allogeneic

Table 1. Patient and sibling characteristics.

Family		Gender	Stage at dx	Age at dx	Paraprotein (PP)	PP-level at dx (g/L)	HLA type		MM-specific therapy	Survival from dx (months)
1										
	p	m	MGUS/IA MM	40/45	IgGκ	46	A3,23(9) B44,35 Cw 04 DQB1 0201, 0202	DRB1 0301, 0701 DRB3 01 DRB4 01	auto-PBSCT	63+
	s	m	MGUS	66	IgGκ	12	A3,26(10) B44(12),13		none	8+
	s	m	MGUS	64	IgGκ	15.7	A3,23(9) B44,35 Cw 04	DRB1 0301, 0701 DRB3 01 DRB4 01 DQB1 0201, 0202	none	47+
	s	f	MGUS	49	IgAκ	5.7	A3,23(9) B44,35 Cw 04	DRB1 0301, 0701 DRB3 01 DRB4 01	none	41+
2										
	p	m	IIA MM	53	IgAκ	3.7	A02 B39,50	DRB1 0701. 1301 DRB3 01 Cw06,12 DRB4 01 DQB1 0202, 0603	MUD PBSCT	74+
	s	f	MGUS/IA MM	61 / 62	IgAκ	9.6	A02 B39,50 Cw06,12	DRB1 0701. 1301 DRB3 01 DRB4 01 DQB1 0202, 0603	standard-dose CX	29+
3										
	p	f	IA MM	61	IgGλ	40.7	A29 B44,58 Cw07,16	DRB1 0701, 0804 DRB4 01 DQB1 0202,0402	auto-PBSCT	54+
	s	f	MGUS	68	IgGκ	14	A29 Cw07,16	DRB1 0701, 0804 B44,58 DRB4 01 DQB1 0202,0402	none	44+
4										
	p	f	IIIA MM	61	IgGκ	22.5	A2,24(9) B14, 37 Cw06,8	DRB1 0102, 0701 DRB4 01 DQB1 0303, 0501	standard-dose CX	8*
s		f	MGUS	70	IgMκ	3.5	A2,24(9) B14,37 Cw06,8	DRB1 0102, 0701none DRB4 01 DQB1 0303, 0501	25+	
5										
	p	m	IIIA MM	57	IgGκ	58.9	A9,19 B7,8 C 07	DRB1 1501, 0301 DRB3 01 DRB5 01 DQB1 0602, 02	auto-PBSCT	60*
	s	m	MGUS/ IIIA MM	52 / 55	IgGκ	16	n.e		standard-dose CX	80*
	s	m	Rai 0 CLL	57	λ	10	A9,19 B27,8		none	36+

*dx: diagnosis ; p: patient; s: sibling; m: male; f: female; λ: λ light chain: κ: κ light chain; n.e.: not evaluated; auto-PBSCT: autologous peripheral stem cell transplantation; MUD: matched unrelated donor; CX: chemotherapy; +: ongoing survival; *: deceased.*

Table 2. Summary of monoclonal B-cell disease.

Number of analyzed families	*Affected members/family*	*Relationship of family members*	*Paraproteins*	*Distinct features*	*Author/ reference*
15	2 MM (12) 3 MM (3)	parent/child (5) siblings (10)	IgG κ/λ [26] IgA κ/λ [4] IgM [1]	genetic factors presumed; family work-up in each case	4
9	2 MM (5) 2-3 MGUS (2) 2 MGUS/MM (2)	parent/child (3) siblings (3) first cousins (3)	IgG [9]+IgA [1] IgA [3] IgM [3] BJP [1]	family members at higher risk than general population	6
8	2 MM (1) 5+5 MM+MGUS (5) 4+4+4 MM+MGUS+WM (2)	analysis of 1st degree relatives and beyond	IgG [10] IgA [4] IgM [6] Ig? [4]	population-based cancer-registry study family registry of 218 MM cases compared with records of Icelandic Cancer registry	7
8	n.e	n.e.	n.e.	serum proteins in relatives	5
5	2-4 MM (3) 3-4 MBCD (2)	parent/child siblings	IgG κ/λ [4] IgA [1] IgM [2] MM n.e. [6] MBCD [2]	genetic anticipation in MM	2
5	2 MM (1) MM+MGUS (3) 2 MM+CLL (1)	siblings	IgG κ/λ [8] IgA κ [3] IgM κ [1] light chain λ.[1] κ/λ: 10:3	dx with screening for allo-PBSCT; similar age of patients and siblings; postulated autosomal-recessive inheritance; therapeutic consequences for pts and donors	Engelhardt M
3	2 MM (3)	n.e.	n.e.	sporadic mutations of p53 gene in MM	Willems PM
3	2 MM (3)	parent/child (2) twins (1)	IgG κ [2] IgAκ/λ [2] BJP κ [2]	high frequency of familial MM in Northern Ireland	Mc Crea AP
4	2 -3 MGUS (4)	n.e.	n.e.	systematic analysis of familial MGUS: 172 relatives+>10000 controls, discussion on relatedness	Youinou P
1	3 MM 2 MGUS	siblings	IgG λ [3] BJP κ[2]	family study+review: Rb-1 locus deletion and translocation; Ø association with chr 11/14	Lynch HT
1	1 MM 4 MGUS	siblings	n.e.	familial occurrence of MM+MGUS: Ø correlation with HLA-type or paraprotein	Bizzaro N
1	3 MM	siblings	IgG κ [2] BJP κ [1]	MM in 3 sibs: Ø association with p53 mutations	Roddie PH
1	2 MM 1 MGUS	siblings	IgM IgG κ / λ BJPλ	systematic sibling analyses, discovery of MM in sister of WM pt	Fine JM
1	2 MM	sisters	BJP κλ	genetic aspects of familial MM: 26 healthy family members; sisters: identical HLA type	Loth TS
1	2 MM	brothers	IgG κ	genetic predisposition+environmental factors	Law MI
1	2 MM	brothers	IgG κ IgA κ	high IgA serum levels in 7/17 family members	Wiedermann D
1	2 MM	father/daughter	light chain λ	high incidence of familial MM	Alexander LL
1	2 MM	mother/daughter	IgG κ	same paraprotein	Comotti B
1	2 MM	father/daughter	IgG κ	association with HLA type: 4c complex, A9	Hubert D
1 (12 case reports) **n=82**	2-3 MM	siblings twins parent-child	n.e.	genetic factors; first case of monozygotic twins; review of 37 families: time interval of dx; family history important	Nadeau LA,Grant JA Klingler W, Herrell WE Horwitz LJ, Judson IR Leoncini DL, Manson DI Schoenfeld Y, Thomas TF

BJP: Bence Jones Proteinuria; MM: multiple myeloma, WM: Waldenström's macroglobulinaemia, CLL: chronic lymphocytic leukemia ( ): number of affected families, [ ]: number of affected persons, dx: diagnosis.

SCT. The investigation included a family history and clinical screening, protein electrophoresis, imaging studies (X-ray, abdominal ultrasound) and HLA-typing. Between 1999 and 2004, we detected five MM patients with one to three siblings showing a previously undetected monoclonal B-cell disease (Table 1). Of a total of 8/27 (29.6%) siblings being affected, seven had monoclonal gammopathy of undetermined significance (MGUS) and one had chronic lymphocytic leukemia. In two out of five families more than one sibling was affected. Two siblings with MGUS developed stage IA and IIIA MM within one and three years, respectively, necessitating treatment. One sibling with stage III MM finally died of progressive disease. The prevalence of monoclonal B-cell disease in asymptomatic siblings of our MM families was 29.6%. From our screening of 134 asymptomatic donors between 1999-2004, the incidence of monoclonal B-cell disease was 8/84 (9.5%) in siblings and 1/50 (2%) in matched unrelated donors. In our MM families, the gender of affected patients and siblings was the same in four out of five families and heavy and light chain paraproteins were predominantly IgG and κ, respectively. The median age at diagnosis was comparable, being 57 years in our five MM patients and 63 years in affected siblings: the median age of the unaffected siblings

was 61 years (p>0.05). Cytogenetic analysis in three out of the five patients revealed a normal karyotype and HLA-typing showed class I subgroup A9 in three out of five families. The median survival of our five MM patients from diagnosis and SCT was 60 (range: 8-74) and 29 (range: 12-37) months, respectively. Three patients are still alive, one with ongoing stable disease, and two in complete remission: one after an allogeneic SCT from a matched unrelated donor and the other after autologous SCT. Two patients have died of progressive disease. Of all MM families, one parent [family #1] is still alive. The others died at a median age of 89 years (range; 57-98). Parents' deaths were of non-malignant causes in all except family #5 (mother died at age 78 of a malignant brain tumor).

Prominent results on familial monoclonal B-cell diseases are summarized in Table 2. The familial occurrence of monoclonal B-cell disease has been described in more than 80 families and familial clustering has previously been suggested.[1-7] Analyses on familial cancer based on the nationwide Swedish Family-Cancer Database[5,6] have described increased standardized incidence ratios (SIR) for various cancers, including MM.[2,3] The SIR of MM in offspring with a parental history of MM was 2.3 (95% CI 1.4-3.5), whereas no increased risk was observed for siblings of MM patients.[2,3] Earlier studies indicated that approximately 10% of MM and MGUS patients can be expected to have relatives with paraproteinemia.[1,4-6,8] Affected siblings in our analysis were all asymptomatic and unexpectedly found to have monoclonal B-cell disease. This is of note, since diagnosis of cancer in family members is likely to alert relatives to seek medical advice. An apparent excess risk has been postulated for prostate, breast, colorectal and skin cancers, for which screening methods are commonly available.[3] Although screening is not routinely performed in *risk*-populations (e.g. siblings prior to allogeneic SCT) this could be easily implemented by serum electrophoresis. The 9.5% prevalence of monoclonal B-cell disease that we found among siblings of MM patients scheduled for allogeneic SCT and the 2% prevalence in matched unrelated donors is noteworthy. This may have resulted from selection, since our cohort was closely examined before allogeneic SCT. Nevertheless, our study was prospective and seems to reflect the actual prevalence of monoclonal B-cell disease. With a prevalence of 29.6% among siblings of our MM families, and of 9.5% among all siblings, an autosomal-recessive inheritance with low penetrance may be postulated. Although genetic and molecular changes of familial monoclonal B-cell disease need to be further defined, our and previous data[1-8] suggest a heritable etiology. With our detection of monoclonal B-cell disease in 2% of matched unrelaetd donors and in and 9.5% of siblings, probabilities for these diseases were five-fold higher in the latter. Our finding of an increased prevalence of monoclonal B-cell diseases in the sibling is also in line with their typically older age than that of matched unrelated donors since the prevalence of these diseases increases with age. It is of interest that the prevalence of monoclonal B-cell disease in our families was also higher than that of MGUS, which is detected in 3% of persons >70 years.[8] We observed a transformation from MGUS to MM in two out of seven siblings and long-term follow-up studies have suggested a transformation rate of 40% within 25 years.[8] This may prove to occur earlier with future analyses, thus making the detection of familial monoclonal B-cell diseases highly relevant.

In summary, familial monoclonal B-cell diseases were detected by examination of siblings offering themselves as allogeneic donors. Our findings had substantial consequences: only one patient received an allogeneic SCT from a matched unrelated donor and siblings were confronted with a diagnosis of cancer, in some cases necessitating treatment. Four recent studies support our findings:[2,7,9,10] two reported a familial risk for MM in first-degree relatives, highlighting the need for systematic studies in order to collect suitable samples for molecular analyses so that genes conferring a predisposition to monoclonal B-cell diseases can be identified.[2,7] Another study detected MM, chronic lymphocytic leukemia and myelodysplastic syndrome in marrow aspirates from asymptomatic allogeneic donors, and suggested intensive screening in older donors and in those with congenital disorders or familial malignancies.[9] Another study offered specific recommendations for the donor work-up[10] and all underlined the need for accurate data collection. Although prospective studies in siblings of large numbers of patients with MM now need to be performed, until these are available, our and previous analyses[1-7] are of clinical relevance, since allogeneic SCT is being increasingly used in malignant and non-malignant diseases and patients receiving such transplants (and their related donors) are now much older.[10] These results and changes in allogeneic SCT practices make screening of patients and donors an important responsibility.

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