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Chronic hepatitis C in long term survivors of haematological malignancy treated in a single centre

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Abstract

***Aims*—To investigate the impact of hepatitis C virus (HCV) infection in long term survivors of haematological malignancy treated before the introduction of blood donor screening in September 1991.**

***Method*—Patients were tested for evidence of HCV infection by third generation enzyme linked immunosorbent assays, a recombinant immunoblot assay and reverse transcriptase polymerase chain reaction. Serum aspartate aminotransferase activities were measured. The number and type of blood component units received by each patient were recorded.**

***Results*—Forty two patients were studied who had received a total of 7143 blood component units. Two patients (4·8%) were found to have HCV infection, both had histological evidence of chronic active hepatitis, and one is now receiving treatment with α-interferon. Both of these patients had been missed by the ongoing look-back programme which aims to detect recipients of all known HCV infected blood components.**

***Conclusion*—Although HCV infection affects a minority of long term survivors of haematological malignancy, infected patients may benefit from α-interferon treatment. The screening of all patients treated for haematological malignancy before September 1991 is advocated.**

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Patients who receive multiple transfusions of blood components from a donor population unscreened for hepatitis C antibodies (anti-HCV) are at risk of developing post-transfusion hepatitis following infection with hepatitis C virus (HCV). Chronic hepatitis occurs in 50% of those infected with hepatitis C[1] and 20% of these develop cirrhosis within 10 years.[2] In the UK screening of blood donors for hepatitis C began in September 1991. Because of the large number of exposures to blood components, patients treated for acute leukaemia or undergoing bone marrow transplantation (BMT) before this date are at high risk of developing transfusion acquired hepatitis C infection. Hepatitis C infection is particularly relevant to this group of patients as some are now long term survivors who are likely to be cured of their original disease.

The aim of this study was to establish the impact of hepatitis C infection on surviving patients, who were either treated for acute leukaemia or were BMT recipients before September 1991.

Methods

The study was conducted at Birmingham Heartlands Hospital, one of two adult BMT units serving the West Midlands. Each year about 15 new cases of acute leukaemia are seen and 25 BMTs (autologous and allogeneic) are carried out. We reviewed the records of all such patients who were treated prior to September 1991 and who are currently disease-free. The number of exposures to donor blood components was recorded. A donor exposure was defined as a single transfused unit of red cells, platelets, fresh frozen plasma, cryoprecipitate, or a platelet aphaeresis pack. Patients were recalled, and informed consent obtained before blood was taken to assess hepatitis C status and assay serum aspartate aminotransferase (AST) activities.

Anti-HCV screening was performed using a third generation enzyme linked immunosorbent assay (EIA, Ortho Diagnostics, Neckargemund, Germany). Reactive samples were further tested using a second EIA (Murex Diagnostics, Dartford, UK) and a recombinant immunoblot assay (RIBA-3, Ortho Diagnostics). All samples were also assessed by reverse transcriptase polymerase chain reaction (RT-PCR) for HCV RNA using the method of Garson *et al.*[3] Anti-HCV positive patients were referred to the regional liver unit for further management.

Data on the prevalence of anti-HCV antibody among blood donors on commencement of testing in 1991 was obtained from the West Midlands Blood Transfusion Service.

Results

A total of 42 patients were assessed (table). A further eight patients may have been eligible (in remission when last seen), but have been lost to follow up. The total number of donor exposures in the 42 patients was 7143, with a mean number of exposures of 170·1 units (range 21–685). The mean time from end of treatment was 6·4 years (range 2·9–14·1). Twenty eight (67%) patients were more than five years from the end of treatment, and therefore likely to have been cured of their original disease.

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Patient characteristics with details of diagnosis, treatment, donor exposures, and hepatitis C status

Patient number	*Age (years)*	*Sex*	*Diagnosis*	*Years from diagnosis*	*Years from end of treatment*	*Treatment*	*Donor exposures*	*Recent AST*	*HCV EIA*	*RIBA 3*	*HCV PCR*
1	68·8	M	AML (CR2)	4·8	2·9	Chemo	217	94	NEG		NEG
2	61·5	M	AML	11·6	10·5	Chemo	168	35	NEG		NEG
3	**69·7**	**M**	**AML**	**7·6**	**7·2**	**Chemo**	**342**	**88**	**POS**	**POS**	**POS**
4	64·2	F	AML	14·3	14·1	Chemo	45	35	NEG		NEG
5	35·5	F	AML (CR2)	11·4	9·7	Chemo	342	16	NEG		NEG
6	52·4	F	AML	9·0	7·7	Chemo	230	15	NEG		NEG
7	54·5	F	APML	8·6	8·0	Chemo + ABMT(×2)	483	22	NEG		NEG
8	63·0	M	AML	4·8	4·4	Chemo	149	28	NEG		NEG
9	62·8	M	AML	5·1	4·7	Chemo	178	54	NEG		NEG
10	70·8	M	AML	7·3	6·7	Chemo	91	18	NEG		NEG
11	58·6	F	AML	11·4	10·5	Chemo	155	23	NEG		NEG
12	**48·8**	**F**	**APML**	**15·5**	**8·9**	**Chemo**	**353**	**67**	**POS**	**POS**	**POS**
13	66·8	M	AML (CR2)	15·0	10·2	Chemo	53	N/A	NEG		NEG
14	52·2	M	APML	6·5	6·1	Chemo	443	33	NEG		NEG
15	44·8	M	APML	4·0	3·0	Chemo + ABMT	222	35	NEG		NEG
16	63·8	M	AML	5·1	4·9	Chemo	116	18	NEG		NEG
17	23·8	F	ALL	9·3	7·2	Chemo	33	15	NEG		NEG
18	25·0	M	ALL	5·4	3·5	Chemo	87	22	NEG		NEG
19	34·6	M	ALL (CR2)	11·8	5·7	Chemo + ABMT	95	38	NEG		NEG
20	34·7	F	ALL	12·5	10·4	Chemo	28	28	NEG		NEG
21	20·5	M	AML/MDS	4·3	3·5	Chemo + ABMT	144	23	NEG		NEG
22	30·3	F	AML	8·0	7·4	Chemo + ABMT	228	21	NEG		NEG
23	59·0	M	ALL	7·6	6·7	Chemo + ABMT	157	22	NEG		NEG
24	33·5	F	AML (CR2)	4·9	2·9	Chemo + ABMT	154	48	NEG		NEG
25	19·7	M	ALL	4·4	3·6	Chemo + ABMT	251	68	NEG		NEG
26	24·1	M	ALL	6·6	5·5	Chemo + ABMT	39	31	NEG		NEG
27	58·5	F	AML	11·5	10·8	Chemo + ABMT	685	47	NEG		NEG
28	38·9	M	CML	6·0	5·8	ALLO BMT	20	50	NEG		NEG
29	40·2	F	CML	5·8	4·2	ALLO BMT	164	23	NEG		NEG
30	26·4	F	HD	4·7	3·7	Chemo + ABMT	47	18	NEG		NEG
31	21·3	M	NHL	4·6	3·0	Chemo + ABMT	78	17	NEG		NEG
32	37·8	M	HD	10·5	6·0	Chemo + ABMT	253	27	NEG		NEG
33	24·1	M	NHL	6·5	6·3	Chemo + ABMT	21	23	NEG		NEG
34	23·0	M	NHL	5·2	4·1	Chemo + ABMT	31	20	NEG		NEG
35	24·2	F	HD	7·0	6·1	Chemo + ABMT	162	20	NEG		NEG
36	23·6	M	HD	9·6	7·7	Chemo + ABMT	30	15	NEG		NEG
37	49·0	F	Plasmacytoma	7·9	6·8	Chemo + ABMT	85	24	NEG		NEG
38	21·9	F	HD	6·9	6·1	Chemo + ABMT	21	N/A	NEG		NEG
39	23·0	M	NHL	4·7	3·8	Chemo + ABMT	47	32	NEG		NEG
40	48·8	M	HD	7·1	6·0	Chemo + ABMT	73	28	NEG		NEG
41	45·5	M	HD	7·4	6·7	Chemo + ABMT	209	29	NEG		NEG
42	51·8	M	HD	6·5	5·2	Chemo + ABMT	414	46	NEG		NEG

AML = acute myoblastic leukaemia; APML = acute promyelocytic leukaemia; ALL = acute lymphoblastic leukaemia; MDS = myelodysplasia; CML = chronic myeloid leukaemia; HD = Hodgkin's disease; NHL = non-Hodgkin's lymphoma; CR2 = second remission; ABMT = autologous bone marrow transplant; ALLOBMT = allogeneic bone marrow transplant; chemo = chemotherapy; AST = aspartate aminotransferase; POS = positive; NEG = negative. Patients with positive results are shown in bold.

Patients 3 and 12 (4·8%) were anti-HCV positive on screening and this was confirmed by the second EIA and RIBA. Both patients were also positive for hepatitis C RNA by RT-PCR. No other patients were positive by RT-PCR. The two HCV positive patients had received extensive blood component support (342 and 353 donor exposures) and were at 7·3 and 8·9 years from completing treatment. At the time of recall, both patients had raised AST activities of 88 and 67 U/l (normal <35 U/l). Histological assessment of liver biopsy specimens showed modified Knodell scores of 5 and 9 (maximum score = 13). Patient 12 is now receiving therapy with α-interferon.

A further eight patients (table) had raised AST activities at the time of recall with a mean of 50 U/l (range 38–94 U/l). Patient 9 was a known hepatitis B carrier; the rest were screened for hepatitis B and found to be negative. Patient 28 has chronic hepatic graft versus host disease, and patient 7 had a liver biopsy carried out which showed siderosis. The liver function of all the above patients is being monitored.

PREVALENCE OF ANTI-HCV IN BLOOD DONORS

In the West Midlands 56 blood donors among a population of about 200 000 (that is, 0·028%) were found to be anti-HCV positive (using a first generation EIA followed by RIBA) at the introduction of screening in September 1991 (personal communication). Donors who showed indeterminate results have been excluded from our calculations as there is accumulating evidence that such individuals are non-infectious.[4,5] Using this data and the number of donor exposures we predicted that one or two (1·8) patients within our group would be HCV positive. It was assumed that 80% of patients receiving a unit of blood from a RIBA positive donor will become infected.[4]

Discussion

The prevalence of hepatitis C infection amongst multitransfused patients with haematological malignancy is low in this study. This is in contrast to both a recent Italian study where 29% (44/102) of children treated for acute lymphoblastic leukaemia were found to be hepatitis C positive[6] and a Finnish study where 17% (12/71) of multitransfused adult patients with leukaemia were positive.[7] The differences between countries seems to reflect the differing prevalence of hepatitis C in the local donor population. The quoted prevalence in Italy being 1·3%[8] and in Finland 0·106%.[6] These are both significantly higher than the prevalence of 0·028% found in the West Midlands. However, it is likely that the prevalence of hepatitis C carriage in blood donors was higher before 1985 when measures were introduced to prevent transmission of HIV via transfusion.[9] The frequency of anti-HCV anti-

body in our study (4·8%) correlates with that found by Murphy *et al* (4·4%) in a group of 183 patients with leukaemia.[10] This is despite their use of a first generation assay, without confirmatory tests. Also, patients in that study were not long term survivors; seven of the eight hepatitis C positive patients had died of recurrent leukaemia.

Unlike previous studies[6,11] we found no patients who were RT-PCR positive and anti-HCV negative. It is likely that immunocompromised patients with HCV will be anti-HCV antibody negative if tested while still immunosuppressed. However, they would be RNA positive by RT-PCR. It would be expected that, with time, their immune systems would recover and anti-HCV be produced. As all of the patients in this study are long term survivors in remission we feel our results are consistent with this theory.

A look-back programme to identify patients who received blood components from known anti-HCV positive donors is underway in the UK.[12] Clearly, this programme will not detect patients who received blood from HCV positive donors who retired prior to the introduction of screening. Significantly, both HCV infected patients identified in this study were missed by the look-back programme.

Cirrhosis is likely to develop in around one fifth of patients with chronic hepatitis.[2] Early identification of such patients is important as treatment with α-interferon can delay progression to cirrhosis; unfortunately, once cirrhosis is established interferon is of little benefit.[13] It is not possible to rely on raised serum aminotransferase activities alone to select patients for hepatitis C testing, as both chronic infection and significant liver disease may be present in the absence of raised activities.[14] Most patients previously treated for acute leukaemia and BMT recipients are followed up indefinitely and are therefore readily accessible for testing. We therefore advocate screening of all such long term survivors for anti-HCV. These patients are at risk of developing life threatening complications of chronic hepatitis C infection many years after being cured of their original disease and, in the UK, the HCV look-back programme will not necessarily detect them.

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