Fludarabine and cytosine-arabinoside for poor-risk acute myeloid leukemia

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Thirteen relapsed or refractory AML patients were treated with the FLA regimen. A complete remission was observed in 54% of cases but the median duration of remission was short (4 months). These results suggest that the FLA regimen is not able to induce a durable complete remission in the poor-risk AML patients.

The non specific multidrug resistance (MDR) is one of the most important causes of treatment failure in acute myeloid leukemia (AML) and is mainly due to the overexpression of 170-Kd trans-membrane glycoprotein (p170).[1] This glycoprotein, coded by the mdr-1 gene, enhances the efflux of several unrelated compounds from the cells and, in doing so, decreases the intracellular drug accumulation and reduces *in vitro* and *in vivo* sensitivity to cytotoxic agents.[2] The availability of agents which are not at all or minimally involved in the MDR efflux mechanism have recently allowed the testing of new therapeutic approaches in AML.[3,4] Fludarabine (Fluda) is a fluorinated purine analogue which is not involved in the MDR efflux mechanism[5] and in combination with Ara-C it showed promising results in AML patients.[6-9] For

Table 1. Clinical and hematological features of 13 poor-risk AML patients before the treatment with Fludarabine in combination with high-dose Ara-C (FLA).

Case	Pt.	Sex/Age	FAB	Months from diagnosis	Previous therapy	Status	Hematological parameters before FLA-treatment WBC x10^9/L	MB % (PB)	MB % (BM)	P170 in BM blasts (MFI)
1.	C.G.	M/67	M2	–	–	Onset	32.	56	60	3.6
2.	G.G.	F/70	M1	–	–	Onset	1.4	0	80	6.5
3.	C.N.	F/53	M2	3	-Ara-C; Idarubicin -Hd Ara-C; Idarubicin -Mitoxantrone; Etoposide; Ara-C	RES	42.	96	90	4.2
4.	C.M.	F/35	Ibrid	4	-Ara-C; Idarubicin -Mitoxantrone; Etoposide; Ara-C	RES	3.2	0	80	3.6
5.	T.I.	M/60	M1	5	-Ara-C; Idarubicin -Hd Ara-C; Idarubicin	RES	12.2	80	80	6.5
6.	G.E.	F/56	M2	2	-Ara-C; Idarubicin	RES	4.2	46	80	8.3
7.	D.F.	M/33	M6	6	-Ara-C; Idarubicin -Hd Ara-C; Idarubicin -Mitoxantrone; Etoposide; Ara-C	I° REL	105.	96	90	7.25
8.	V.G.	F/54	M1	11	-Ara-C; Idarubicin -Hd Ara-C; Idarubicin -Mitoxantrone; Etoposide; Ara-C	I° REL	11.8	76	90	4.8
9.	C.F.	F/56	M2	10	-Ara-C; Idarubicin -Hd Ara-C; Idarubicin -Mitoxantrone; Etoposide; Ara-C	I° REL	9.8	39	90	8.4
10.	S.S.	F/34	M2	30	-Daunorubicin; Etoposide; Ara-C -Hd Ara-C; Idarubicin -Mitoxantrone; Etoposide; Ara-C -Busulfan; Cyclophosphamide (ABMT)	I° REL	24.	13	60	5.3
11.	D.M.	M/22	M1	14	-Ara-C; Idarubicin -Hd Ara-C; Idarubicin -Busulfan; Cyclophosphamide (BMT) -Mitoxantrone; Etoposide; Ara-C	II° REL	1.0	0	80	4.6
12.	S.R.	M/38	M2	10	-Ara-C; Idarubicin -Hd Ara-C; Idarubicin -Busulfan; Cyclophosphamide (BMT) -Ara-C	II° REL	1.0	0	80	11
13.	P.F.	M/22	M0	52	-Daunorubicin; Etoposide; Ara-C -Vincristine; Prednisone -Hd Ara-C; Idarubicin -Hd Ara-C; Idarubicin;Vincristine; Prednisone -Busulfan; Cyclophosphamide (ABMT) -Mitoxantrone; Etoposide; Ara-C	II° REL	2.3	1	60	3.1

RES = Resistant; REL = Relapse; PB = Peripheral Blood; BM= Bone Marrow; MFI = Mean Fluorescence Index.

Table 2. Clinical response to FLA regimen and its correlation with the p170 expression (MFI).

Case	S	P170 in BM blasts (MFI)	FLA 1st course	Resp.	P170 in BM blasts (MFI)	FLA 2nd course	Resp.	Follow-up CCR	OS	S
1.	onset	3.6	yes	CR	–	–	–	4	6	Died
2.	onset	6.5	yes	res	15.6	–	–	–	11	Died
3.	res	4.2	yes	res	4.5	–	–	–	1	Died
4.	res	3.6	yes	CR	–	–	–	1	5	Died
5.	res	6.5	yes	res	6.8	–	–	–	4	Died
6.	res	8.3	yes	CR	–	yes	CR	8	8	Alive
7.	1st rel	7.2	yes	res	10.5	–	–	–	2	Died
8.	1st rel	4.8	yes	res	3.8	–	–	–	6	Died
9.	1st rel	8.4	yes	CR	–	yes	CR	5	8	Alive
10.	1st rel	5.3	yes	CR	–	–	–	2	7	Died
11.	2nd rel	4.6	yes	CR	–	–	–	2	5	Died
12.	2nd rel	11	yes	res	12.5	–	–	–	1	Died
13.	2nd rel	3.1	yes	CR	–	–	–	8	10	Alive

S = status; resp. = response; res = Resistant; rel = Relapse; CR = Complete Remission; CCR = Continuous Complete Remission; OS = Overall survival.

these reasons we treated 13 relapsed or refractory AML patients with the FLA regimen consisting of five days of treatment with a 30-minute infusion of Fluda 30 mg/sqm/day, followed four hours later by a 4-hour infusion of cytosine arabinoside (Ara-C) 2 g/sqm/day (Table 1). As reported in other studies[6-9] we observed a complete remission (CR) in a relative high proportion of cases (54%), but the median duration of remission was short (4 months) (Table 2). Before therapy, the p170 expression in bone marrow blasts was evaluated by an indirect immunofluorescence method with the anti-p170 monoclonal antibody MRK-16 and the results were expressed as the *mean fluorescence index* (MFI).[2] Six out of 13 patients (46%) were overexpressing the p170 glycoprotein (MFI > 6.0) and only two reached a CR (cases 6 and 9) (Table 2). Out of the 6 patients who had the MFI < 6, five patients reached a CR. All patients experienced a severe myelosuppression but the non-hematological toxicity was mild and the most common side effects were nausea and vomiting (WHO grade I or II). The median time of granulocyte recovery (ANC > 500/uL) was 22 days (range 12-35) and a platelet count > 50,000/uL was reached after a median of 22 days (range 14-34). During the neutropenic phase 9 (69%) patients developed microbiologically or clinically proven infections. However, none of them developed opportunistic infections except one, who developed a lethal mucormycosis when he apparently was in CR. These results suggest that the FLA regimen is myelotoxic but not able to induce a durable complete remission in the poor-risk AML patients, such as the relapsed or refractory ones. Further studies should be performed in order to define whether or not p170-positive leukemic cells can escape Fluda and Ara-C cytotoxicity, or alternatively, if these agents may select cells with different mechanisms of resistance.[10] Since the non-hematological toxicity of FLA regimen was mild, the addition of a third agent like idarubicin, which is slightly involved in the MDR efflux mechanism, could be considered in an attempt to strenghten the antileukemic activity of the FLA regimen.

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Key words

Acute myeloid leukemia, treatment, fludarabine, cytosine-arabinoside

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Therapy-related acute leukemia associated with involvement of 11q23 after high grade non-Hodgkin lymphoma

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Therapy-related acute myeloid leukemias with balanced translocations affecting the 11q23 chromosome region are one of the most serious complications of treatments with topoisomerase II inhibitor drugs as epipodophillotoxins and anthracyclines.1, 2-5 These cases are usually associated with short interval time from previous chemotherapies, absence of myeloid dysplastic phase, hyperleukocytosis and young age. We and others have recently identified and cloned the ALL1 gene at 11q23 band (also named MLL, HRX, Hrxt) which is consistently altered in t-AML following therapies with topo II targeting drugs.1 However, there are few reports of cases of t-AML, clinically and biologically similar to the subtype of leukemias secondary to exposure to topo II inhibitors drugs but without the involvement of the ALL1 gene. These observations suggest that genes other than ALL1 which are etiopathogenetically relevant for hematological neoplasias are located in this cytogenetic region.

A 27-year-old man was admitted to our institution in June 1994 with a 4-week history of fever, anorexia and weight loss. Chest X-ray and CT scan showed a mediastinal mass with enlargement. A bone marrow (BM) aspirate and biopsy revealed normocellular BM. The diagnosis of high-grade B-cell lymphoblastic NHL with sclerosis was made on a needle biopsy of the mediastinal mass. No cytogenetic analysis was done on the BM at diagnosis. The clinical stage was defined as IA *bulky*.

From September 1994 to January 1995 the patient received 11 courses of the MACOP-B chemotherapy with cytosine arabinoside, vincristine, adriablastine, methotrexate and etoposide, achieving only partial remission due to the persistence of 20% of the initial mediastinal mass.[3,4] Local radiotherapy (RT) (3600 cGY/fac, with inverted fields) was administered from March to April 1995. One week after the end of RT, an hemochromocytometric analysis revealed 19×10^9/L WBC with 98% of blasts with monocytic features. At this time the BM biopsy showed a total substitution by leukemic blasts. On the basis of standard morphological, immunological and cytochemical criteria a diagnosis was made of acute myeloid leukemia, FAB M4. The karyotype was 46 XX, t(7;11) (p21;q23), t(10;X) (p14;q24). The ICE protocol was administered as treatment of AML without achieving a CR.[2] The patient died from infective complication in June 1995.

An ALL1 germline genomic configuration was detected by Southern blot analysis of DNA from both the mediastinal mass at the time of diagnosis of NHL and from BM leukemic blasts at the onset of AML. To this purpose DNA was digested to completion with *Bam* HI and *Hind* III endonucleases and hybridized with the B859 probe, which is a cDNA insert containing the ALL1 exon 5-11 sequences.

Our case report allows us to draw some possible etiopathogenetic suggestions on t-AML leukemogenesis. Firstly, the observation from the literature that none of the rare cases of NHL with 11q23 developed a t-AML rule out the hypothesis that t-AML represents an evolution of the natural history of the disease.[7,8] It is well known in fact that t-AML after NHL is a serious complication of treatments including topo II inhibitors drugs usually with consistent involvement of the ALL1 gene at 11q23.[3] Moreover, the identification within the ALL1 breakpoint cluster region of DNA structures involved in the topo II machinery, such as high-affinity scaffold attachment regions and topoisomerase II binding sites, has provided a strong pathogenetic linkage in this leukemic subset between chemotherapeutic agents and targeting gene.[6]

However, the observation that the ALL1 gene is not always altered in cases with clinical, biological and cytogenetic features similar to those of ALL1+ t-AML suggests that in the 11q23 cytogenetic band gene(s) other than ALL1 could exist that are involved in the pathogenesis of t-AML. In this respect, it is interesting to note at least two other genes implicated in hematological malignancies which have been identified within this cytogenetic region: namely, the p54/RCK gene found altered in two B cell malignant lymphomas with t(11;14) (q23;q32) cytogenetic translocation, and the PLZF gene coding a ZF protein which is fused to the RARA in acute promyelocytic leukemia with t(11;17)(q23;q21) abnormality.[6-10]In conclusion, the present case provides further evidence of the need to search for other gene(s) located in this region which could be involved in the pathogenetic mechanism leading to t-AML after exposure to chemotherapeutic treatments.

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Non-Hodgkin's lymphoma, 11q23, acute leukemia

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Achromobacter xylosoxidans bacteremia in patients with hematologic malignancies

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We report nine cases of *Achromobacter xylosoxidans* bacteremia diagnosed in patients with hematologic malignancies. There was not an obvious epidemiologic link between cases and the organism was not isolated from any source. Outcome was cure in all nine cases. In our experience, catheter removal is generally required for eradication of *A. xylosoxidans*.

Achromobacter xylosoxidans is a non-fermenting gram-negative rod widely distributed in the environment, like hospital fluids, from which outbreaks of nosocomial infections may occur.[1-3] About 90 cases of *A.xylosoxidans* bacteremia have been reported, twenty-one out of these in patients with hematologic malignancies, though eleven occurred as an infectious outbreak in a hematology ward.[4-6]

Between January 1993 and April 1997, the data of 8 patients from the department of hematology who suffered *A.xylosoxidans* bacteremia were recorded. One patient had two infections separated by 8 months and has been included twice.

Tables 1 and 2 show the patients characteristics of the series. All cases of bacteremia were not related with each other by time or space and *A.xylosoxidans* was not isolated in hospital environment nor any other source than blood cultures. Patients received empiric broad spectrum antibiotics and they were changed if resistance was demonstrated.

None of the patients developed septic complications or deep-seated infections, suggesting that *A.xylosoxidans* is a non-virulent organism even in highly compromised hosts. Six isolates were sensitive to ampicillin and eight to amoxicillin-clavulanate. Six cases were resistant to all first and second generation cephalosporins and two to ceftazidime. All species were resistant to gentamicin and tobramicin and two cases were sensitive to amikacin. On the other hand, susceptibility to the fluorquinolones, ticarcillin, piperacillin and carbapenems was universal. One case was resistant to co-trimoxazole.

A.xylosoxidans is an infrequent human pathogen, but various different types of infections have been reported, including primary bacteremias and deep-seated infections in normal individuals or patients with multiple underlying conditions.[7,8]

Although *A.xylosoxidans* bacteremia is uncommon, we have observed nine episodes in the last four years. During this period, 541 adult patients received intensive chemotherapy and 40 cases of non-fermenting

Table 1. Patient characteristics. I.

Cases	Sex/ age	Underlying disease	Recent BMT (days)	Severe neutropenia	In-patient
1	M/22	NHL	APBSCT (+3)	yes	yes
2	M/40	CML	APBSCT (+3)	yes	yes
3	M/40	HD	ABMT (+2)	yes	yes
4	M/27	ALL	ABMT (+3)	yes	yes
5	F/33	ALL	none*	yes	no
6	M/46	AML+GVHD	BMT (49 months)	no	no
7	M/46	AML+GVHD	BMT (57 months)	no	no
8	M/59	MM	APBSCT (+3)	yes	yes
9	M/43	HD	APBSCT (+2)	yes	yes

**Consolidation chemotherapy. NHL: non-Hodgkin's lymphoma; CML: chronic myelogenous leukemia; HD: Hodgkin disease; ALL: acute lymphoid leukemia; AML: acute myelogenous leukemia; GVHD: graft-versus-host disease; MM: multiple myeloma; APBSCT: autologous bone marrow transplantation; BMT: allogeneic bone marrow transplantation.*

Table 2. Patient characteristics. II.

Pts.	Catheter infection	Primary treatment	Response	Secondary treatment	Outcome
1	yes	imipenem+amikacin	refractory	CR	cure
2	yes	imipenem+amikacin	refractory	CR	cure
3	yes	imipenem+amikacin	cure	none	cure
4	yes	ceftazidime+amikacin	refractory	CR	cure
5	yes	ceftazidime+amikacin	relapse	CR	cure
6	yes	ceftazidime+amikacin	cure	none	cure
7	yes	CR	cure	none	cure
8	no	clinafloxacin+CR	cure	none	cure
9	yes	imipenem+amikacin	refractory	CR	cure

CR: catheter removal.

gram-negative infections were documented, including the 9 cases of *A.xylosoxidans* reported herein (1.6% of all patients). This bacteria can be found in aqueous environments, such as disinfectants and fluids. Thus, we might suspect in a common source, but there was no epidemiological relationship between cases. Moreover, three episodes were diagnosed as outpatients.

In our series, the majority of patients had severe neutropenia, and it is possible that mucositis and breakdown of the intestinal barrier allowed invasion of bloodstream by *A.xylosoxidans*. Clinical presentations were highly persistant fever and chills, but neither death nor sepsis syndrome occurred despite poor response to antibiotic therapy in most cases. This is in contrast with other non-fermenting gram-negative infections, which are often associated with high morbidity and mortality.[9]

The antibiotic susceptibility profile of isolates was similar to previous reports,[4,5] with special emphasis on the almost universal *in vitro* resistance to aminoglycosides and aztreonam. As with other non-fermenting gram-negative bacilli, most isolates were susceptible to broad-spectrum β-lactams, co-trimoxazole and fluoroquinolones. The most important conclusion, from our experience, is that these infections are usually catheter-related, and despite their apparently low morbidity, removal of the catheter is generally required for definitive eradication of the microorganism. Appropriate *in vitro* antibiotic therapy may be ineffective or lead only temporary control of the infection.

Key words

Bacteremia, hematologic malignancies

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Unexpected late graft failure 9 months after HLA-identical bone marrow transplant (BMT) for chronic myeloid leukemia (CML): treatment with a second BMT

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We describe a patient with CML in 1st chronic phase (CP) who experienced a graft failure 9 months after an HLA genotypically identical sibling BMT. Drug toxicity, viral infections, chronic graft-versus-host-disease (GVHD) or leukemic relapse were excluded. Chimerism study showed 85% of donor marrow cells. She underwent a second BMT, reengrafted but died of grade IV acute GVHD.

Late graft failure (LGF) after allogeneic BMT is defined as pancytopenia with marrow hypoplasia after complete engraftment.[1] It is observed after haploidentical or T-cell-depleted BMT and in heavily transfused aplastic anaemia patients receiving identical grafts.[2,3] The reported incidence of this event is about 0.4%.[3] Cyclosporine withdrawal, interferon-α treat-

ment, human herpes virus-6 (HHV-6) infection, chronic GVHD, increasing recipient's age or lower dose of BM cells infused,[1,4-7] have been implicated.

A 44-year-old female was diagnosed of CML in CP on July 1993. She was treated with hydroxyurea and subsequently interferon-α2b for 24 months without cytogenetic response. On January, 1996, she underwent a BMT from her genotypically identical brother conditioned with busulphan (16 mg/kg) and cyclophosphamide (120 mg/kg) and 4.81×10^8 unmanipulated bone marrow (BM) mononuclear cells (MNC) per kg of recipient were infused. GVHD prophylaxis consisted of cyclosporine and short methotrexate. She reached complete engraftment with complete cytogenetic chimerism on day +90. Chronic GVHD screening was negative and cyclosporine was withdrawn on day +180. On day +258, isolated thrombocytopenia of 61×10^9/L was detected, that evolved to pancytopenia (leukocytes 0.6×10^9/L, hemoglobin 9.6 g/dL and platelets 2×10^9/L) in 12 days. Physical exam revealed fever and herpetic lesions on nose and lips. Biochemical parameters, including serum B_{12} and folic acid levels, liver function tests and LDH, were normal. Autoimmunity screening, Coombs' and Ham's tests were negative. Chest-x-ray was normal. Red blood cell group and antigens were of donor type (O^+). A marrow aspirate was very hypocellullar with lymphocytes, hystiocytes, plasma cells and mastocytes. Genomic amplification studies by PCR in marrow specimen were negative for herpes viruses (HSV-I and II, CMV, EBV, HZV, HHV-6) and Parvovirus B19. BM cariotype was 46 XY and RT-PCR of bcr/abl transcripts was negative. Chimerism study by PCR of VNTR loci on MNC from BM revealed 85% of MNC of donor and 15% of receptor. Hemotherapy, broad spectrum antibiotics, amphotericin-B and acyclovir were administered.

Idiopathic LGF was diagnosed. She underwent a second BMT from the same brother conditioned with cyclophosphamide (50 mg/kg/day for 4 days) and ATG (30 mg/kg/day for 3 days), with infusion of 4.6×10^8 unmanipulated marrow MNC per kg of recipient 17 days after LGF observation. Cyclosporine with short methotrexate were again given. She recovered $>1.0\times10^9$/L neutrophiles on +15 and $>50\times10^9$/L platelets on +40. Acute GVHD of skin and liver developed and she was treated with corticosteroids (2 mg/kg/day). On +33, she was discharged in good condition with 6.8×10^9/L leukocytes and 43×10^9/L platelets. BM karyotype was 46 XY and 100% of BM cells were of donor origin. She was readmitted on day +51, with nausea, vomiting and slight diarrea. Intravenous nutrition and increased immunosuppression were given under suspicion of GVHD progression. CMV antigenemia was detected and Gancyclovir started. Her condition worsened, with liver function deterioration (bilirubin 40 mg/dL), gastrointestinal bleeding and hepatic encephalopathy. She died on day +75. Autopsy was denied.

LGF has been rarely described after unmanipulated grafts for CML.[5,6] In previously reported cases of LGF occurring more than 6 months after BMT, a cause could be found (T-cell depletion, HHV-6 infection, chronic GVHD or leukemic relapse).[5,6,8] The mechanism of LGF is unknown.[11] Residual host lymphocytes with *in vitro* inhibitory effect against donor hemopoietic cells have been sometimes detected.[6] Second transplants have a high transplant-related mortality in this condition[2,10] and immunosuppression treatment alone or combinated with stem cells reinfusion or hematopoietic growth factors.[1,4,5,8,9] frequently induce autologous hematopoietic recovery.[1,8]

In our patient, a second BMT was decided because of the long interval between first BMT and graft failure and good patient's performance status. Engraftment was successful but lethal GVHD developed. The optimal approach to manage this complication is unclear and reports are scarce and heterogeneous.

Key words

HLA-identical BMT, chronic myeloid leukemia, graft failure

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Primary orbital lymphoma: contralateral relapse after six years in complete remission

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We report a patient diagnosed of an intermediate-grade primary orbital lymphoma with relapse in the other orbit after six years in complete remission (CR).

Primary orbital lymphoma (POL) comprises about 5-10% of all orbital neoplasms.[1] Most common symptoms are exophtalmus and diplopia.[2] POL is usually diagnosed at early stage, and shows low to intermediate-grade histology. Radiotherapy (36-40 Gy) is a successful treatment in most patients, so this entity has a favorable prognosis, with long free disease survival.[3-5] However, we report a patient diagnosed of an intermediate-grade POL with relapse in the other orbit after six years in complete remission (CR).

A 35-year-old man with persistent right exophtalmus and visual impairement, was diagnosed of intermediate-grade POL after undergoing biopsy of a retrocular mass. The extension of disease was evaluated by computerized tomography (CT) scan and magnetic resonance (MR). No other lymphomatous locations were found. CR was achieved after systemic chemotherapy and local radiotherapy (40 Gy). After 6 years, left exophtalmus was noticed. A left orbital mass was detected by MR. The histological examination revealed the same intermediate-grade pattern.The imaging diagnosis showed no spread disease. Chemotherapy and radiotherapy were administered. Nowadays the patient remains in CR.

We have not found any other reference in the literature about contralateral relapse of POL. However, although POL usually shows indolent course and good prognosis, we suggest a long term folllow up, in order to diagnose late relapse .

Key words

Orbital neoplasms, relapse, extranodal lymphoma

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Recent advances in myelodysplastic syndromes (MDS)

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This year Haematologica reports a series of review articles on *Recent Advances in Myelodysplastic Syndromes*: the first one appeared in the January issue,[1] the second one is found in this issue.[2] Future articles will analyze prognostic factors, secondary MDS and therapy of these disorders. The basis for this series has been the *Fourth International Symposium on Myelodysplastic Syndromes* held in Barcelona, Spain, on April 24-27, 1997. The Meeting organizers – Guillermo F. Sanz, Miguel A. Sanz and Teresa Vallespi – have done a remarkable job as Guest Editors. In 1997 Haematologica published several articles on MDS[3-12] and is now proud of publishing this series, which will hopefully appear also as a separate print and electronic volume.

Key words

Myelodysplastic syndromes

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Transfusion-associated *Red Eye syndrome*

Since December 1997, the Centers for Disease Control and Prevention (CDC) has received approximately 100 reports, from 10 different states, of patients who have developed severe conjunctivitis within 24 hours of transfusion. To date, all reported reactions have been associated with receipt of leukocyte-depleted red blood cells. In addition to "red eyes", many patients have experienced ocular pain, periorbital edema, arthralgias, and headache. The symptoms have generally resolved within 2 to 14 days after onset; no permanent sequelae have been reported.

The CDC, Food and Drug Administration, and blood bank officials are conducting investigations to determine the potential etiology and extent of these reactions. Health care providers, blood bank personnel, and local health officials should report all confirmed, or suspected, cases of transfusion-associated red eye syndrome to the CDC's Hospital Infections Program by phone at (404) 639-6413 or by fax at (404) 639-6459.

Centers for Disease Control and Prevention