Volume 308, number 1, 4-6 FEBS 11381 August 1992
© 1992 Federation of European Biochemical Societies 0014-5793/92/$5.00

Bleomycin-reactive iron in patients with acute non-lymphocytic leukemia

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Received 23 June 1992

Bleomycin-reactive iron was detected in the sera of six out of nine adults undergoing intensive chemotherapy for acute non-lymphocytic leukemia. In these individuals the corresponding transferrin saturation ranged from 96% to 113% and the serum ferritin from 775 to 9975 μg/l. Nontransferrin-bound iron has been postulated to be a factor in organ toxicity in iron overload conditions such as beta thalassemia and hereditary hemochromatosis by facilitating the production of tissue-damaging free radicals. We propose that bleomycin-reactive iron should be considered as a possible factor in organ dysfunction seen with intensive cancer chemotherapy.

Non-transferrin bound iron; Acute non-lymphocytic leukemia; Cancer chemotherapy; Free radicals; Serum iron; Serum ferritin

1. INTRODUCTION

In iron overload conditions such as β thalassemia and hereditary hemochromatosis, an abnormal fraction of serum iron that is not bound to transferrin has been postulated to be a factor in organ toxicity [1,2]. Such nontransferrin-bound iron might facilitate the production of free radicals that promote damage to lipids, proteins and DNA [3-6]. Patients treated with intensive cancer chemotherapy for acute non-lymphocytic leukemia regularly experience marked elevations in serum iron concentrations and transferrin saturations [7] that are similar to values observed with iron overload. These patients often experience hepatic [8], pulmonary [9,10], and other organ dysfunction that may not be clearly related to chemotherapeutic agents, infections, or other identifiable causes. The capability of bleomycin to degrade DNA in the presence of ferrous iron [11] has been used as the basis for an assay to measure iron not bound to transferrin or ferritin in plasma of patients with iron overload [12,13]. Halliwell and colleagues found bleomycin-reactive iron in plasma samples from six subjects who were treated for acute non-lymphocytic leukemia [14]. Such an abnormal iron fraction might be a potential cause of some organ toxicity. We examined the sera of nine patients with acute non-lymphocytic leukemia for the presence of bleomycin-reactive iron before, during and after intensive chemotherapy.

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2. MATERIALS AND METHODS

Serial serum samples were prospectively obtained with informed consent from patients undergoing chemotherapy for acute non-lymphocytic leukemia at MetroHealth Medical Center or University Hospitals of Cleveland. Nontransferrin-bound iron was measured using the bleomycin assay [13] as described, except that sera was used instead of plasma. Serum iron and total iron binding capacity (TIBC) were measured using methods of the International Committee for Standardization in Hematology, modified to be used for small quantities of serum [15,16], and transferrin saturation was calculated. Serum ferritin was measured using FER-IRON immunoradiometric assay kits (Ramco Laboratories, Inc., Houston, TX).

3. RESULTS

Nine patients were studied (Table 1), including seven males and two females with ages ranging from 24 to 64 years. Seven patients received induction chemotherapy regimens (two for initial treatment, five for relapsed leukemia) and two patients were given consolidation therapy. Chemotherapeutic drugs included cytosine arabinoside (8 patients), daunorubicin (5 patients), 6-thioguanine (3 patients), amsacrine (1 patient), mitoxantrone (1 patient) and etoposide (1 patient). Duration of chemotherapy ranged from 5 to 9 days, median 7.

Bleomycin-detectable iron was identified in the sera of six of the nine patients from 1 to 6 days after chemotherapy was started. Before onset of chemotherapy only two patients had bleomycin-reactive iron. In two patients with bleomycin-detectable iron, repeat analysis demonstrated that it persisted on day 11. In all of six patients tested 12 to 29 days after onset of chemotherapy no bleomycin-reactive iron was found.

At the time bleomycin-detectable iron was found, the corresponding transferrin saturation was greater than 95% in all but one serum sample.

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4. DISCUSSION

Over one-half of patients with acute non-lymphocytic leukemia who are treated with intensive chemotherapy develop elevations of hepatic enzymes [9,17]. Although these patients receive multiple blood products and are at a high risk for transfusion associated viral hepatitis, not all hepatic dysfunction is clearly related to this etiology. Some patients develop hepatic veno-occlusive disease, a condition that is not typical of viral hepatitis and has high mortality. Among patients undergoing bone marrow transplantation for malignancy, up to 21% develop hepatic veno-occlusive disease [18,19].

Unexplained pulmonary dysfunction is also common in patients treated with intensive cancer chemotherapy. In an autopsy series of patients with leukemia at Johns Hopkins Hospital, 42 of 51 patients who had received chemotherapy within 30 days of death had evidence of pulmonary edema [10]. In one-third of these, a cause (i.e. infection, cardiac failure, renal failure, aspiration) for the pulmonary edema could be found, but two-thirds of the cases were idiopathic. The investigators attributed those pulmonary abnormalities to cytosine arabinoside toxicity, but the evidence for this was only circumstantial. In another series from the National Cancer Institute studying antibiotic therapy in cancer patients with fever and neutropenia, 6 of 33 deaths were due to pneumonitis and respiratory failure of undetermined cause [11]. In three recent studies documenting the occurrence of adult respiratory distress syndrome in neutropenic patients [20–22], most of the patients reported were cancer patients who had recently received chemotherapy.

Our data suggest that, in patients treated with intensive cancer chemotherapy, the circulation may be presented with iron in excess of what can be bound to the highly saturated transferrin molecules, and that in some patients iron that is detectable by the bleomycin assay is present. In most of these patients there are markedly elevated serum ferritin concentrations (Table 1) that most likely are related, at least in part, to lysis of leukemic cells and release of tissue ferritin. Although Pootrakul and colleagues [23] have proposed that iron contained in plasma ferritin is an explanation for non-transferrin iron, the bleomycin assay reportedly does not detect iron contained in concentrated solutions of ferritin that is fully saturated with iron [13].

Under normal circumstances circulating iron is tightly bound to transferrin so that there is virtually no free iron in the plasma [13]. The presence of iron not bound to transferrin in the serum is distinctly abnormal and might cause formation of the highly reactive and damaging hydroxyl radical leading to peroxidation of membrane lipids and tissue damage [3,24]. We propose that circulating bleomycin-reactive iron should be considered as a possible factor in some cases of hepatic, pulmonary, and other dysfunction seen during intensive chemotherapy. Iron chelation conceivably might be protective for some toxicity seen in patients with acute non-lymphocytic leukemia [25].

Acknowledgements: This investigation was supported in part by a grant from the Department of Medicine, Cleveland Metropolitan

Table 1

Bleomycin-reactive iron in sera of patients treated for acute non-lymphocytic leukemia

	Day after onset of chemotherapy											
	−1 to 0			1 to 6			11			12 to 29		
Patient	Bleomycin-detectable iron (μM)	Transferrin saturation (%)	Ferritin (μg/l)	Bleomycin-detectable iron (μM)	Transferrin saturation (%)	Ferritin (μg/l)	Bleomycin-detectable iron (μM)	Transferrin saturation (%)	Ferritin (μg/l)	Bleomycin-detectable iron (μM)	Transferrin saturation (%)	Ferritin (μg/l)
1	0	66	3375	0	101	5302				0	47	2228
2	3	99	1769	4	105	845				0	37	3292
3	0	23	574	4	96	775						
4	0	22	1820	3	102	2119	2	100	739			
5	0	34	670	2	99	1768	3	102	1538			
6	0	61	345	0	59	3110				0	99	3609
7	0	86	1200	0	72	4699				0	55	1152
8	0	44	2000	8	103	9975				0	89	1078
9	0.5	80	2877	2	113	4075				0	93	3321

General Hospital, and by Public Health Service Grant P30CA43703 awarded by the National Cancer Institute, Department of Health and Human Services.

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