Phenotype Switch in Acute Leukemia Patients After Intensive Chemotherapy

R. Ihle, H. Matthes, and H. Ihle

A. Introduction

With the aid of monoclonal antibodies it has become possible to improve the correct diagnosis and classification of acute leukemias. From the literature and from our own experience we know that there is a distinct percentage of patients in whom the leukemic blasts express markers of different blood cell lineages. These so-called mixed-lineage leukemias are mostly associated with a poor prognosis in relation to the other cases. Besides the mixed lineage, we know that a lineage switch in the course of relapsing or resistant acute leukemia patients is also possible. This is perhaps important for the correct treatment of these patients.

B. Material and Methods

In the past few years we have analyzed our acute leukemia patients with a panel of 20 monoclonal antibodies which were kindly provided by Prof. Walter Knapp from the University of Vienna, Austria, with support of the International Society of Chemo- and Immunotherapy, Vienna. The antibodies used are listed in Table 1. The methods are described elsewhere [1, 2]. In a group of 64 patients with acute leukemia we performed simultaneously morphological, cytochemical, and immunocytological investigations in order to classify the leukemias. We diagnosed 49 as AML and 15 as ALL. The age ranged from 15–79 years. These investigations were also performed in the cases of relapsing or resistant disease.

The treatment of patients with acute myeloid leukemia was performed according to the TAD schedule after Gale and Cline, the treatment of ALL with a modified Hoelzer scheme. In cases of resistant or relapsing leukemia in patients under the age of 50 years we tried to give an intensive high-dose cytarabine AraC treatment, administering 3 g/m^2 twice daily over 6 days in combination with 45 mg/m^2 daunorubicin over 3 days.

C. Results

Of 64 patients with acute leukemia we found 49 to have AML and 15 to have ALL. In five patients (7.8%) there was a biphenotypical expression of myeloid and lymphoid markers. Three patients (4.7%) showed a lineage switch during the course of the disease (Table 2).

Following are the case reports in brief:

Case 1: Patient S. K., female, 17 years old. In April 1985 an M2 type of AML was diagnosed and treated according to the TAD schedule. A complete remission (CR) was achieved, but the patient refused an autologous bone marrow transplantation. Over a period of 6 months we performed a consolidation treatment,

Department of Internal Medicine, Division of Hematology, University Hospital Charité, Humboldt-Universität Berlin, German Democratic Republic

Abbreviation TAD = Thioguanine: 200 mg/sqm p.o. for 7 days Ara-C (Cytosinearabinoside): 200 mg/sqm i.v. for 7 days Daunorubicin: 60 mg/sqm for 3 days

Table 1. Our panel of monoclonal antibodies and their specificity (provided by Prof. W. Knapp, Vienna, with the support of the International Society of Chemo- and Immunotherapy, I.G.C.I., Vienna)

Cluster		Antibody	Specifity
B-cell marker	CD10	VIL-A1	Common-ALL antigen
	CD24	VIBC5	Pre-B, B cells, granulocytes
		VIBE3	Pre-B, B cells, granulocytes
T-cell marker	CD3	VIT3b	T cells
	CD1	VIT6	Cortical thymocytes
	CD4	VIT4	T-helper
	CD8	VIT8	T-suppressor
		VIT12	T cells
Myelomonocytic marker	CD15	VIMD5	Granulocytes
		VIM2	Granulocytes, monocytes
	CD11	VIM12	Granulocytes, monocytes
	CD14	VIM13	Monocytes
Erythroid marker		VIEG4	Glycophorin A
Platelet marker		VI-Pl1–3	Platelets, megakaryocytes
Proliferation marker		VIP1	
		VIP2b	
HLA-DR marker		VID1	HLA-DR

Table 2. Lineage switch in three patients with acute leukemia in the course of disease

Patient	Antibody (% positivity of blast cells)															Diagnosis
	CD10	VID1	CD24	CD1	CD3	CD4	CD8	VIP1	VIP2b	CD15	VIM2	CD11	CD14	VIEg4	VIP11–3	
K.S.	–	10	30	–	–	–	–	–	–	70	40	25	20	–	–	M2-AML
	60	50	90	–	3	1	1	–	10	5	2	–	–	–	–	Common ALL
M.K.	–	20	60	–	10	10	10	5	3	90	90	10	8	–	–	M2-AML
	80	95	95	–	–	–	–	–	–	5	2	2	–	–	–	Common ALL
G.H.	–	90	70	8	15	10	10	40	35	20	24	3	20	–	–	B-ALL
	–	5	5	–	–	–	–	5	20	10	60	30	40	–	–	M4-AML

and then the treatment was stopped. In May 1986 a myeloid relapse was again treated with TAD. Again a complete remission was achieved. After the second relapse in October 1986 we administered a 6-day course of high-dose AraC. Only a partial remission was achieved. The blast cells were now morphologically undifferentiated, and an immunological diagnosis of common ALL was made. Despite continuous treatment the patient did not achieve complete remission. She died in April 1988.

Case 2: Patient M. K., female, 33 years old. In July 1985 an M2 type of AML was diagnosed. After three TAD courses a complete remission was achieved. She relapsed in November 1985, again with an M2 type. After repeated TAD a CR

was achieved, continuing until September 1986. The morphologically undifferentiated blast cells now exhibited characteristics of a common ALL. No therapeutic benefit was possible, and the patient died 1 month later.

Case 3: Patient G. H., male, 65 years old. Between 1979 and 1983 a cyclophosphamide regimen for a glomerulonephritis was administered. Thereafter, the patient became pancytopenic. In November 1985 an acute lymphoblastic leukemia of the B-cell type was diagnosed. A modified Hoelzer therapy was performed, but there was only a partial response to the therapy. At the end of January, 1986, the cytomorphological pattern changed and we diagnosed AML of the M4 type morphologically as well as immunologically. A TAD therapy was not effective and the patient died in March 1986.

D. Summary and Conclusions

According to Stass et al. [4] the percentage of a lineage switch occurs in 6.7%–8.6% of patients with acute leukemia. Mostly, a conversion from the lymphoid to the myeloid phenotype is seen. In our three cases we found two switches from the myeloid to the lymphoid phenotype and only one from lymphoid to myeloid. This lineage switch is seen in relapsing and resistant leukemia cases [3].

Different hypotheses have been discussed concerning the phenotype switch. Cytostatic chemotherapy may eradicate one leukemic cell clone, allowing another one to proliferate. Otherwise, the leukemic transformed stem cell could be influenced by the chemotherapy, resulting in a change of the differentiation program of the cell and following with a switch of marker expression. Perhaps there is some clinical importance to monitoring the phenotype switch in order to administer the best treatment.

References

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