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Plasminogen Activator as a Prognostic Factor in Hematological Malignancies

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A. Introduction

The plasminogen–plasmin system is involved in many physiological processes such as fibrinolysis, tissue remodelling, destruction of intercellular matrix and cell migration [1]. Human cells release plasminogen activators of two distinct immunochemical types – urokinase and tissue plasminogen activator [2–4]. The activity of these enzymes in biological systems is regulated by a variety of agents such as hormones, retinoids and tumour promoters [5–11]. It is also regulated by protease inhibitors such as protease nexins [12] and by receptors for the enzyme on the surface of human fibroblasts [13]. Leukaemic cells secrete both species of plasminogen activator and patients with acute myeloid leukaemia whose cells release only tissue plasminogen do not respond to combination chemotherapy [14].

B. Methods

Heparinized blood samples were obtained from 117 patients with acute myeloid leukaemia (AML), from 31 patients with chronic myeloid leukaemia (CML), and from 89 patients with other myeloproliferative disorders. Cells were isolated by centrifugation on Ficoll–Hypaque and resuspended in RPMI containing 3% foetal calf serum to give 4×10^6 cells/ml [14]. The medium was harvested by centrifugation 24 h later and stored at – 80 °C for analysis of enzyme activity. Plasminogen activators were assayed by measuring the plasminogen-dependent release of soluble radioactive fibrin degradation peptides from insoluble ^{125}I-labelled fibrin-coated multiwell dishes as previously described [15]. Molecular species of plasminogen activators were identified by electrophoretic and immunochemical procedures as previously described [2].

C. Results and Discussion

Immunochemical analysis showed that granulocytes from 23 normal individuals released urokinase exclusively. Cells from 24/117 patients with AML secreted tissue plasminogen activator, cells from 67/117 patients secreted urokinase, cells from 14/117 patients secreted a mixture of both enzymes and cells from 12/117 patients secreted too little enzyme for identification (Table 1). The molecular species of enzyme appeared to have prognostic significance since none of the patients whose cells secreted tissue plasminogen activator entered remission with chemotherapy whereas remission was induced in 80% of patients whose cells secreted urokinase. There was a significant difference in median survival between those patients whose cells secreted tissue plasminogen activator (5 weeks) and those individuals whose cells secreted

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Table 1. Correlation between clinical outcome and molecular species of plasminogen activator released by cultured cells from 117 patients with AML

Therapy	Group	Response	Nature of plasminogen activator				Totals
			TA[a]	UK[b]	TA and UK	Unknown	
Combination chemotherapy	A	Assessment completed					
		Complete remission	0	32	7	5	44
		No remission	14	10	2	1	27
		(Subtotals)	(14)	(42)	(9)	(6)	(71)
	B	Died before assessment	5	14	4	3	26
No/palliative therapy	C		5	11	1	3	20
Totals			24	67	14	12	117

[a] TA tissue activator
[b] UK urokinase

urokinase (32 weeks). No significant differences in age or white blood cell count at the time of presentation were found between those patients whose cells secreted tissue plasminogen activator and urokinase. Cells from approximately 20% of patients with AML secreted tissue plasminogen activator.

Cells from 31 patients with CML were examined for species of plasminogen activator produced. Cells from 15/31 patients secreted tissue plasminogen activator, cells from only 7/31 secreted urokinase and cells from 9/31 secreted both species of enzyme. Thus, the proportion of patients with CML whose cells secreted tissue plasminogen activator was much higher than in the AML group and cells from only 23% of these individuals secreted urokinase.

Cells isolated from 89 patients with other myeloproliferative and preleukaemic disorders have also been investigated. Cells from 47/89 patients secreted tissue plasminogen activator, cells from 16/89 patients secreted urokinase and cells from the remainder secreted both enzyme species. Thus, the myeloproliferative disorders contain a far higher percentage of individuals whose cells secrete tissue plasminogen activator – the enzyme which is associated with a failure to respond to chemotherapy in patients with AML. This is of interest as it is well known that when patients with CML or myelodysplastic states transform, they have a poor prognosis and do not respond to chemotherapy. We are investigating the plasminogen activator status of our patients with myeloproliferative disorders at regular intervals in order to ascertain whether those patients with tissue plasminogen activator have a worse prognosis than those patients whose cells secrete urokinase. It appears as if the type of plasminogen activator secreted by leukaemic cells cultured in vitro will serve as a useful aid to prognosis for patients with AML and possibly also for patients with other myeloproliferative disorders.

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