FLT3 - ITD positive acute lymphocytic leukemia, does it impact on disease´s course?

FLT3 – ITD pozitif akut lenfositik lösemi hastalığının gidişatını etkiliyebilir mi?

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To the Editor,

Fms- like tyrosine kinase 3 (FLT3) - internal tandem duplication (ITD) has been identified in up to 25% of all acute myeloid leukemia where it correlates with a very poor prognosis [1]. Since FLT3 is frequently expressed by acute lymphocytic leukemia (ALL) blasts, activating FLT3 mutations may as well occur in this disease [2]. According to the literature, only 14 of 1634 ALL-patients were tested positive for FLT3-ITD (Table 1) [2-8]. Unfortunately, survival data of those patients is lacking and conclusions on the impact of FLT3-ITD in ALL patients are inconsistent. However - in analogy to AML- it has been suggested that FLT3-ITD dramatically worsens patient´s survival [8].

We report of a 42-year-old woman with a FLT3-ITD PCR positive common B-ALL. No established negative prognostic factors were found; therefore the patient was considered at standard risk. The patient achieved a complete remission after the first course of conventional induction chemotherapy. Importantly, assessment of a patient specific molecular minimal residual disease (MRD) by PCR was repeatedly performed and scored negative. Since the first control at day 28, none of the patient specific markers could be detected. 8 months later, the patient is still in complete remission. Accordingly, FLT3-ITD might not necessarily be associated with a worse outcome.

Interestingly, for all FLT3-ITD positive ALL patients where an adverse outcome had been described, other

Table 1. Overview on studies reporting FLT3-ITD- positive ALL patients and their outcome

# patients screened	Study population	# FLT3-ITD +	Risk factors	Outcome	Reference
60	adults	4	high LDH, high blast count	73.7% vs 84%* complete remissions	[2]
132	children	1	relapsed ALL	N.S.	[3]
60	children	2	biphenotypic ALL	44 and 72 months	[9]
174	children	1	none	alive at time of report	[5]
143	children	2	N.S.	N.S.	[6]
63	N.S.	2	biphenotypic ALL, high blast count	poor	[7]
449	adults	2	CD117 positive	N.S.	[8]

*: FLT3+ vs FLT3- N.S.: not specified

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negative prognostic factors such as bi-phenotypic leukemia + [7, 9], c-Kit expressing T-ALL [8] or relapsed ALL [3] have been reported. Several authors even reported no deterioration of overall survival for FL3-ITD positive standard risk ALL patients (Table 1). In addition, it has been proposed that the prognosis might be correlated with high levels of FLT3 on leukemic blasts rather than with FLT3-ITD in ALL patients [2].

In the present case of a patient with common B-ALL, FLT3-ITD did not seem to impact the patient's prognosis. This assumption is based on the persistently negative MRD assessment more than 8 months after treatment's start. A negative MRD on week 10 most strongly correlates with a prolonged remission and cure [10]. In fact, the MRD negative group has a projected 75% cure rate [10].

In summary, ALL with FLT3/ITD might not be associated with a poor prognosis, although the very low incidence of this molecular alteration in ALL prevents a definite conclusion. Larger prospective series are necessary to finally clarify the prognostic significance of FLT3 mutations in ALL.

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