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Original article

Prognostic factors for therapy-related acute myeloid leukaemia (t-AML) – A single centre experience

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ABSTRACT

Prognostic parameters for treatment outcome in 42 consecutive patients with t-AML diagnosed and treated in a single centre between 2000–2010 (mean age: 56.07 years, range: 23–84; 30 females) were evaluated retrospectively/prospectively. Antecedent malignancy occurred in 37 patients (88.15%): 28 solid cancers (breast, $n = 14$), nine haematological. History of previous chemotherapy (CT), radiotherapy (RT) alone and combined CT/RT was present in 42.9%, 6.19% and 30.1% patients, respectively. Primary disease was active in 11 patients (six relapsed or metastatic cancers; five autoimmune diseases). Myelodysplastic syndrome preceded t-AML in 29% of patients. Median latency period from prior CT/RT was 54.62 months (range: 6–243). Median WBC count was 27.23×10^9/L, platelet count 62.29×10^9/L, haemoglobin level 87.83 g/L, peripheral blood and bone marrow blast percentage 30.7% and 66.7% respectively, serum LDH 1216 U/L. Aberrant expression of B or T lymphoid markers was registered in seven out of 39 and six out of 39 patients, respectively. Aberrant karyotype was detected in 24 out of 33 (72.7%) of eligible patients: favourable: 15.2%, intermediate: 42.4% and unfavourable: 42.4%. Eastern Cooperative Oncology Group (ECOG) performance status greater or equal to 2 and Haematopoietic Cell Transplantation Specific Comorbidity Index (HCT-CI) greater or equal to 3 exhibited 83.3% and 76.2% patients, respectively. Intensive induction CT for t-AML was administered in 24 patients. The median follow-up and the median overall survival (OS) for the whole cohort were 2 months and 5.94 months (range: 0.5–34), respectively. In 10 patients (23.8%) achieving complete remission (CR), median disease free survival (DFS) was 11.8 months (range: 4–32). Only CD19 expression, pretreatment karyotype, ECOG PS, HCT-CI and activity of primary disease had impact on OS ($P < 0.05$).

1. Introduction

Therapy-related acute myeloid leukaemia (t-AML) is the most serious late complication after cytotoxic therapy for malignant or non-malignant diseases. This entity, accounting up to 10% of all AML cases, is considered to have poor prognosis [1,2]. As most of patients have received several classes of cytotoxic agents, the current World Health Organisation (WHO) classification abandons prior categorization according to the type of previous treatment [1]. Chromosomal aberrations and unfavourable karyotype are more frequently seen in t-AML than in *de novo* AML [3,4]. Additionally, the outcome in t-AML proved to be inferior within all cytogenetic risk groups compared to *de novo* AML [5–7]. As most of the patients with t-AML are already heavily pretreated, host-related factors such as poor performance status (PS) and chronic comorbidities might contribute to their dismal prognosis [8]. Regarding this issue, the treatment algorithm based on patients' PS and clonal abnormalities is proposed [2].

As only a small proportion of patients with history of prior cytotoxic treatment develop t-AML, it is suggested that genetic susceptibility [9] and epigenetic changes, such as polymorphism of genes included in DNA repair [10] or drug metabolism [11,12] may contribute to its pathogenesis.

Although aetiology and pathobiology of t-AML are now better understood, there are only a few reports concerning clinical aspects of t-AML [4,13–17]. Therefore, the aim of our study was to evaluate the prognostic significance of various patient-related and disease-related parameters on t-AML outcome.

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2. Patients and methods

2.1. Patients

Forty-two consecutive adults with t-AML diagnosed and treated at Clinic of haematology between 2000–2010 were retrospectively/prospectively analyzed. They were selected from a cohort of 650 consecutive adults with AML, seen at the same period. Diagnosis of t-AML was based on WHO 2008 [1] criteria together with well-documented data of previous chemotherapy (CT) and/or radiotherapy (RT) for antecedent disorder. All patients gave informed consent for all diagnostic procedures and treatment according to the Declaration of Helsinki. Recorded patient-related and leukaemia-related parameters are shown in Tables 1–4. PS was assessed using Eastern Cooperative Oncology Group (ECOG) scale [18]. Comorbidites were scored according to modified Haematopoetic Cell Transplantation Comorbidity Index (HCT-CI) [19]. AML was categorized according to French-American-British (FAB) criteria [20].

2.2. Immunophenotyping

Cell surface membrane antigen analysis was performed on heparanized bone marrow specimens by using indirect immunofluorescence and flow cytometry methods (EPICS-C, Coulter or FACScalibur, Becton Dickinson) as previously described [21]. Commercial monoclonal antibodies (BD Biosciences, USA) were organised in a two-, three-, or four-color panels, including evaluation of surface membrane (CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD11c, CD13, CD14, CD15, CD16, CD19, CD22, CD24, CD33, CD34, CD36, CD41a, CD45, CD56, CD61, CD64, CD66b, CD71, CD117, CD235a, HLA-DR) and intracellular antigens (CD3, MPO, CD79a, TdT). Blast cell populations were sequentially gated and analyzed according to forward and side scatter characteristics (FSC/SSC) only (2000–2006) or in combination with pattern of CD45 antigen expression and SSC cell characteristics (CD45/SSC) (2007–2010). Regularly we collected at least 10,000 blast cells per gate per tube. Results were considered positive by a criterion of greater or equal to 20% labelled cells for membrane as well as greater or equal to 10% for intracellular antigens. For most markers positivity criterion was at least 20% leukaemic cells expressing the marker, except for intracellular antigens for which a lower cut-off has been applied (10%) as recommended [22].

2.3. Cytogenetic analysis

Cytogenetic analysis was carried out either directly or after short-term culture of bone marrow cells for 24–48 hours, according to HG banding method [23]. The karyotypes were designated according to the ISCN [24] and further categorized into favourable-, intermediate- and unfavourable-risk group according to Grimwade et al. [25].

2.4. Treatment

Patients were treated with one out of four following modalities: intensive induction therapy (regimen 1) consisting of daunorubicin at a daily dosage of 45 mg/m^2, on days 1–3, in combination with cytarabine at 200 mg/m^2 daily as a continuous intravenous infusion for 7 days (3 + 7 regimen), except for patients with acute promyelocytic leukaemia treated with PETHEMA LPA-99 [26]; induction therapy with 50% reduced doses of daunorubicin (regimen 2), palliative therapy with hydroxyurea or etoposide, applied per os (regimen 3), and transfusions and antibiotics on demand (regimen 4). Bone marrow response status was determined as recommended [27]. None of our patients underwent allogenic stem cell transplantation as there were no available donors. Response was established by proposed criteria [22]. Overall survival (OS) was defined as the time from diagnosis of AML to death from any cause or date of the last follow-up. Disease free survival (DFS) was defined as the time from achieving complete remission (CR) to relapse or death from any cause or date of the last follow-up.

2.5. Statistical analysis

Data were summarized by frequency and percentage for categorical variables. For continuous variables, the medians and range were computed. For statistical analysis in differences, χ^2 or

Table 1
Baseline characteristics of the 42 patients with t-AML.

Characteristics	Value	CR rate	Cox regression	OS	DFS
		Logistic regression		Log rank	Log rank
		P value	*P* value	*P* value	*P* value
Sex – *n* (%)		0.91	0.56	0.52	0.48
Male	12 (28.6)				
Female	30 (71.4)				
Age (years), range	56 (23–82)	0.30	0.83		
<60 – *n* (%)	29 (69)	0.13	0.30	0.25	0.053
≥ 60	13 (31)				
18–49	12 (28.6)	0.11	0.45		
50–59	17 (40.4)				
60–69	8 (19.1)				
70+	5 (11.9)				
EF – *n* (%)	36 (85.7)	1.00	1.00	0.84	0.89
$\geq 50\%$	1 (2.4)				
$<50\%$	5 (11.9)				
Performance status – *n* (%)		0.06	0.05	0.01	0.07
ECOG 0,1	7 (16.7)				
ECOG ≥ 2	35 (83.3)				
HCT-CI – *n* (%)		0.06	0.06	0.03	0.06
<3	10 (23.8)				
≥ 3	32 (76.2)				

EF: left ventricle ejection fraction; ECOG: Eastern Cooperative Oncology Group; HCT-CI: Hematopoietic Cell Transplantation Specific Comorbidity Index.