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Time Elapsed from AML Diagnosis to Induction Chemotherapy Affects Overall Survival*

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ABSTRACT

We aimed to study the effect of elapsed time from AML diagnosis to treatment (TDT) on OS in a group of patients from public Hospital in Brazil. 41 AML (23 M, 18 F, 41 yrs, 18 - 84 yrs, from 2001 to 2004). There were 38 de novo AML and 3 secondary, median TDT was 6 days (range 1 - 82 d); the young ones were treated earlier than old ones (TDT 4 days vs 11, p = 0.07). Longer TDT (>10 d) was associated with worse CR rates (p = 0.02) and OS (p = 0.04). When patients were categorized into TDT from 1 - 4 d (I) vs >5 (II), those from I presented better OS than II (p = 0.004). When TDT was longer than 7 days OS decreased even more. Hb was higher in patients with TDT I vs II (8.3 vs 7.5 g/dL, p = 0.03) but WBC (p = 0.34) and platelet count (p = 0.75) were not different. Patients with TDT of 10 d were younger than TDT > 10 d (median age 41 vs 70 yrs, p = 0.001). The OS was 15.1% in 2 yrs and 8.6% in 7 yrs. Our data suggest longer TDT, when analyzed continuously, predicted for lower CR rates and OS rates.

Keywords: Acute Myeloid Leukemia; Karyotype; Time to Induction; Elderly AML; Prognostic Factors

1. Introduction

Acute Myeloid Leukemia (AML) is a heterogeneous group of genetically diverse hematopoietic malignancies arising from blood cell progenitors. The management of AML represents a significant clinical challenge to haematologists and, although the incidence of the disease is relatively low, the clinical resources needed for its successful management are substantial (including, but not limited to early chemotherapy initiation, aggressive large broad antibiotic usage, early antifungal prescription, red blood cell and platelet transfusions) and consequently it is considered an oncologic emergency. The outcome for patients with AML depends greatly on the age of the patient and leukaemic cell karyotype and therefore different treatment strategies may be appropriate for different sub-groups of patients. To date, other key prognostic factors are *FLT3-ITD* status and response to induction chemotherapy [1-3]. Usually, AML patients present at diagnosis with severe infections and other worsening medical conditions that demand prompt treatment [3]. Due to AML nature and the need for immediate treatment induction chemotherapy is given simultaneously during medical treatment of other conditions or short-delayed until life-threatening conditions are treated and medically managed and stabilized.

With regards to the time elapsed from AML diagnosis to the start of induction chemotherapy few new data were published specially in emergent countries in which the overall context is very unique due to limited resources and availability of specialized hematological care [4-7]. In this paper we aimed to study retrospectively the effect of elapsed time from AML diagnosis to treatment (TDT) on overall survival OS in a group of patients from the public academic institution Hospital São Paulo, Brazil.

2. Material and Methods

Forty-one consecutively AML patients were consecutively studied (23 males and 18 females, median age: 41 yrs, range 18 - 84 yrs) from Jan 1st, 2001 to Mar 31st, 2004. Last overall survival assessment was done on Jul

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24th, 2011. AML diagnosis was set according to WHO classification and by G-banding karyotype (ISCN, 2009). Cytogenetic risk classification categories were adapted from MRC [1]. Patients were treated with 3 + 7 daunorubicin (45mg/m^2/d/3d), APL patients received ATRA-based regimen [8]. The study was approved by the institution ethics committee. Kaplan-Meier and student t-test were used.

3. Results

Initially fifty-eight consecutive patients were studied. However seventeen patients unfit for intent to treatment chemotherapy due to poor medical conditions and were managed with supportive care onlu (e.g. blood and platelet transfusions, antibiotics, management of medical conditions, hydroxurea in patients with leukcocytosis).

The remaining thirty-eitght patients were analysed given all of them received induction therapy. There were 38 patients with *de novo* AML and 3 secondary (**Table 1**), the median pretreatment WBC was 9.1/μL (range 0.5 - 240/μL), median TDT was 6 days (range 1 - 82 d); 26 patients were young (<60 yrs) and 15 old (>60 yrs) (**Tables 2** and **5**). Cytogenetic risk distribution was: favorable 20.7%; intermediate 27.6%; unfavorable 27.6% and no metaphases 27.6%. Twenty patients achieved CR (48.7%): 61.5% in the young and 26.6% in the elderly group, respectively. Median overall survival was significantly greater in young than elderly patients (291 vs 88 days, respectively, p = 0.003, **Figure 1** and **Tables 3**-**5**). There were no statistical differences with regards to biological features (Hb, WBC and platelet count) between two age groups (**Table 2**). Interestingly, young patients tended to be treated earlier than old ones (TDT 4 days vs 11, p = 0.07 **Table 5**). Moreover, there was noticed an inverse correlation in TDT with age, leukocyte, CR and OS (**Table 4**). Longer TDT (>10 days) was associated with poorer CR rates (p = 0.02) and OS (p = 0.04). When patients were categorized into specific TDT groups: early (1 - 4 days: I) and late (>5 days: II), those from I presented better OS than II (p = 0.004). When TDT was greater than 7 days OS decreased even more. Hb was relatively higher in patients with TDT I vs II (8.3 vs 7.5 g/dL, p = 0.03) but WBC (p = 0.34) and platelet count (p = 0.75) were not different. Patients with TDT of 10 d were younger than TDT > 10 d (median age 41 vs 70 yrs, p = 0.001). For the entire AML cohort OS was 15.1% in 2 yrs and 8.6% in 7 yrs.

Table 1. Patient demographics.

Characteristics		AML patients n (%)
Total		58
Disease	AML *de novo*	51 (88.8%)
	AML secondary	7 (12%)
Sex	Male	29 (50.0%)
	Female	29 (50.0%)
Induction therapy	Induction chemotherapy	41
	Supportive care	17
Complete remission		70.6%
Cytogenetic risk group		
	Favorable	12 (20.7%)
	Intermediate	16 (27.6%)
	Unfavorable	14 (24.1%)
	NA	16 (27.6%)

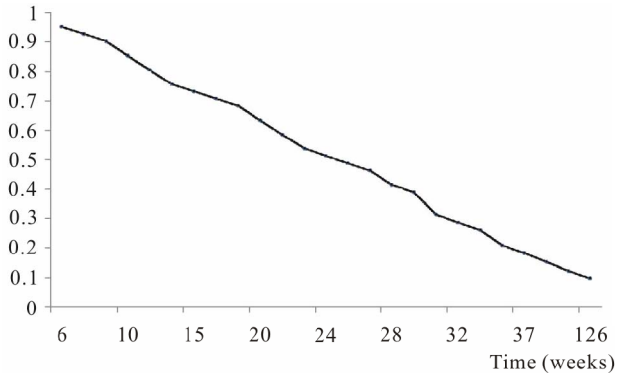

Figure 1. Cumulative overall survival in AML patients.

Table 2. Time to induction AML, overall survival and baseline hematology parameters.

Time to induction (days)	Number of patients	OS (weeks)	Median age (yrs)	Median Hb (g/dL)	Median leukocyte × 10^9/l	Median platelet × 10^9/l
1	5	285	41	8.1	8	38
2	6	122	45.5	7.7	9.65	63.5
3	3	37	50	8.9	12.1	35
4	4	181	35	6.15	8.1	59
5 - 6	4	161	48	8.15	8.4	42.5
7 - 9	6	26	56	5.3	18.7	44
>10	13	11	70	6.9	3.9	53

Table 3. Time to induction AML and overall survival.

Time to induction (days)	Number of patients	OS (weeks)	p value
1	5	285	
2	6	122	
3	3	37	
4	4	181	
5 - 6	4	161	
7 - 9	6	26	
>10	13	11	p = 0.04

4. Discussion

The results showed that less than half of the patients reached CR. Younger patients presented better CR than

Table 4. Time to induction chemotherapy and complete remission.

Time to induction (days)	Number of patients	Complete remission	p value	Comparison	p value
1	5	60%		1 - 4 days vs >5 days	0.004152
2	6	83.3%	0.00993272		
3	3	66.6%			
4	4	50%			
5 - 6	4	25%			
7 - 9	6	33.3%			
>10	13	38.4%	0.47		

Table 5. Comparison between time to induction and age groups.

	<60 years	>60 years old	total	p value
Median days with complaints in medical history	21	30	30	0.06
Median time to treatment	4 days (1 - 45)	11 days (2 - 82)	6 days	0.079
Median leukocyte $\times 10^9$/l	9	9.3	9.25	0.79
Median Hb g/dL	7	7.25	7.4	0.26
Median platelet $\times 10^9$/l	38	27	51	0.33
Overall survival (days)	291	88		0.003
Favorable	10	2	12	
Intermediate	5	3	8	
Unfavorable	6	3	9	
No metaphases	5	7	12	

elderly and this is similar to other series [3,5,9,10]. Despite chemotherapy regimen younger patients presented poorer OS compared to Northern Hemisphere patient series [3,10]. Several reasons may account for such results: poorer performance status at diagnosis, delayed diagnosis (patients could be seen elsewhere or given blood/platelet transfusions in other clinics), and presenting bleeding and infectious complications at diagnosis, advanced disease (severe marrow failure, poor physical reserve). Elderly patients who were treated presented dismal OS and notably a median TDT almost three times longer than younger. Reasons for a longer TDT in AML in the elderly group were: significant comorbidities, severe infectious complications, and delayed start chemotherapy due to logistics reasons (access to chemotherapy, the need to involve caregivers and family members to aid in decision-making process. With more comorbidity in elderly population, reluctance toward intensive therapy is common and probable medical decision is critical in this scenario. Thereupon measures to shorten the TDT should be taken: address a rapid AML diagnosis, evaluate and treat comorbidities, and develop a supportive and continuous system to promote early AML diagnosis and prompt treatment. Our data suggest that longer TDT, when analyzed continuously, predicted for lower CR rates and OS rates, hence we need to address identify factors and start therapeutic measures to aid decision making and improve OS in AML patients in our country.

Authors and Affiliations

Contribution: LAFP, wrote the paper, analysed data and followed up patients. MLC is in charge of the Leukemia Sector of Hematology Department and oriented treatment and follow up of patients as well as contributed to drawing the study and the paper. MY performed diagnosis, SSR analysed data.

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