MIXED-PHENOTYPE ACUTE LEUKEMIA (MPAL): BIOLOGICAL PROFILE, CLINICAL CHARACTERISTIC AND TREATMENT OUTCOMES. REPORT OF A COHORT-BASED STUDY

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INTRODUCTION

MPAL represents an uncommon but heterogenous disease arising from precursor stem cell co-expressing more than one lineage-specific markers. The aim of this retrospective study was to describe the clinical and biological characteristics of our series.

PATIENTS AND METHODS

We retrospectively analyzed 27 patients diagnosed as biphenotypic leukemia by immunopthotype according to EGIL or WHO criteria between 2000-2020. The flow cytometry immunophenotyping (FCM) study were performed in bone marrow aspiration (BMA) samples. Statistical analysis was performed using IBM SPSS version 26 to estimate Overall Survival (OS) and Event Free Survival (EFS) using Kaplan-Meier curves and differences between groups are compared with the log-rank test

RESULTS

Among the 27 patients included, 11 cases were excluded by accomplish other WHO entities (5 therapy related myeloid neoplasm and 6 myelodysplasia related changes AML) and 16 patients who fulfilled the EGIL biphenotypic or the MPAL WHO 2017 criteria were included in the analysis.

Table 1. Immunophenotype diagnosis of cases according to EGIL and WHO

	Total (n=16)	EGIL (n=16)	WHO (n=11)
MPAL B/M NOS †	10	10 (90%)	7 (70%)
MPAL T/M NOS ±	2	2 (100%)	2 (100%)
MPAL t(9;22) (q34.1;q11.2);BCR-ABL1 *	4	4 (100%)	2 (50%)
MPAL t(v;11q23.3); KMT21A-rearranged	0	0 (0%)	0 (0%)
Acute undifferentiated leukemia	0	0 (0%)	0 (0%)
Total (%)	16 (100%)	16 (100%)	11 (69%)

† 2 patients bilineal leukemia (100% B/M), 8 patients biphenotypic B/M
± 1 patient bilineal leukemia (T/M), 1 patient biphenotypic T/M
* 1 patient bilineal leukemia (B/M), 3 patients biphenotypic B/M

Table 2. Clinical, biological and transplant characteristics of the complete cohort and allogeneic HSCT subset

Characteristic	Total (n = 16)	Allo-HSCT patients (n = 8)
Age (years), median (range)	47,9 (12 – 86)	37.5 (12 – 52)
Gender		
Male	8 (50)	3 (37.5)
Female	8 (50)	5 (62.5)
Leucocyte count, median (range)	30.16 x 10^9 /L (0.7 – 168)	28.72 x 10^9 /L (3.5 – 168)
Platelet count, median (range)	102.7 x 10^9 /L (10 – 292)	112.5 x 10^9 /L (25 – 292)
Hemoglobin (g/dL), median (range)	9.3 (5.6 – 16.5)	9.6 (5.6 – 12.4)
LDH (U/L), median (range)	1087 (159 – 3752)	881 (159 – 2130)
Blast cells (%)		
PB	43 (0-98)	53.6 (0 – 98)
BM	85 (65-99)	82.7 (65 – 98)
Extramedullary disease (%)	5 (31.3)	3 (37.5)
CNS	3 (18.8)	2 (25)
Adenopathy	1 (6.3)	-
Visceromegaly	1 (6.3)	1 (12.5)
Cytogenetics (%)		
Normal	5 (31.3)	4 (50)
t(9;22) BCR-ABL1	4 (25)	3 (37.5)
Hyperploid	5 (31.3)	-
Clonal	1 (6.3)	1 (12.5)
Non-evaluable metaphases	1 (6.3)	-
Treatment approach		
ALL-directed chemotherapy	8 (50)	6 (75)
AML-directed chemotherapy	6 (37.5)	2 (25)
Supportive care	2 (12.5)	-
Chemorefractoriness, n (%)	6 (37.5)	5 (62.5)
No. of induction courses, median (range)	1.5 (0 – 4)	2.1 (1 – 4)
Disease status at transplant		
CR MRD^{neg}		3 (37.5)
CR MRD^{pos}		3 (37.5)
Active disease		2 (25)
Donor type, n (%)		
MRD		2 (25)
MURD		6 (75)
PB stem cell source, n(%)		8 (100)
Graft versus host disease		
Acute		6 (75)
Chronic		3 (37.5)

Half of the patients (n=8) received ALL-directed chemotherapy, 6 cases AML-based chemotherapy and 2 only supportive care. Among 8 patients (50%) who received ALL-directed chemotherapy, 5 (63%) achieved CR1, 1 (13%) died during induction due to infectious complication and 2 (24%) patients received rescue therapy (one of them underwent to allo-HSCT in active disease achieving CR, relapsing as granulocytic sarcoma one year later, and the other patient is currently in CR2).
Within the 6 patients (38%) that received AML-directed chemotherapy, 2 cases (34%) achieved CR1 (one patient underwent autologous stem cell transplantation (ASCT) and is in remission after 8 year of follow-up and the other patient received high dose cytarabine as consolidation, relapsing after 14 months) and 4 patients (66%) showed refractoriness. Among refractory patients, 2 cases required rescue treatment and underwent to allo-HSCT, one in active disease status and the other in CR, dying both after 3 and 7 months due to post-transplant complications). The other 2 refractory patients (25%) died due to treatment-related complications.
Considering all treatment approaches together, 8 out 16 patients achieved CR after induction therapy, 6 of them consolidated with allo-HSCT, 1 with ASCT and the remaining patient with chemotherapy. Furthermore, 2 additional patients underwent to allo-HSCT in active disease status so, in our series, half of patients (8) underwent to transplant, being alive and in CR in 4 cases (50%).

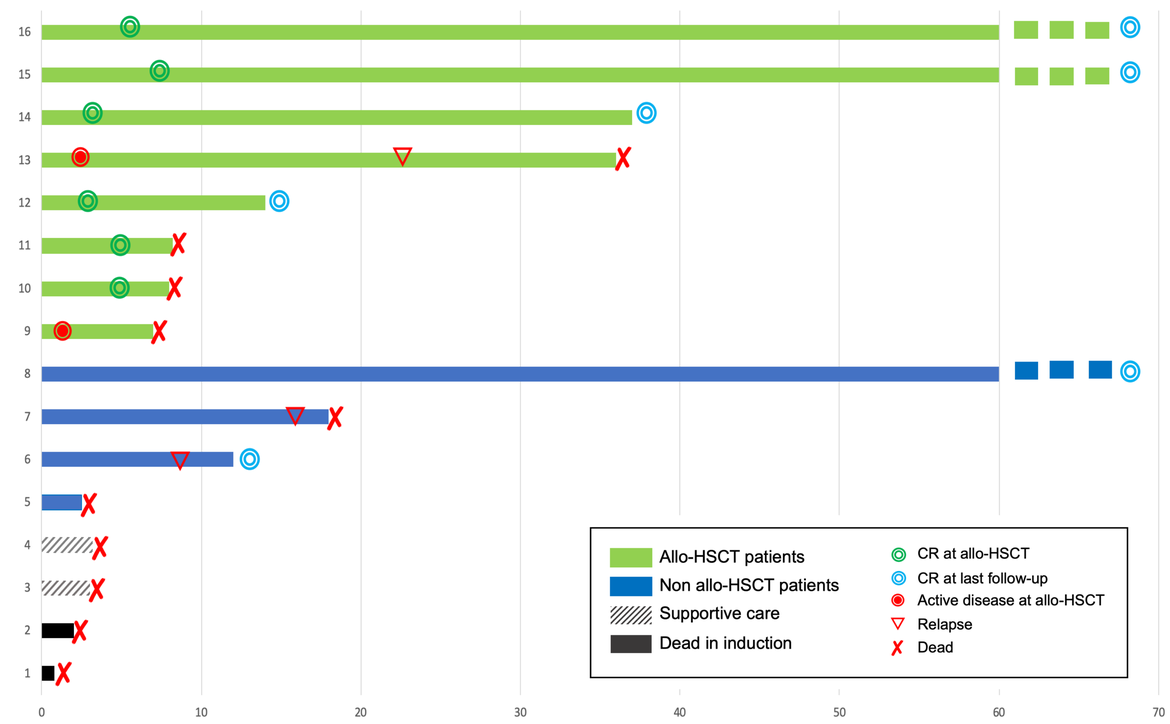

Figure 1. Time from diagnosis to last follow-up in months of our cohort

At the last follow up (June 2020), 6 patients (38%) maintains CR and the remaining patients (n=10, 62%) died (6 due to relapse / progression and 4 by other causes).
The 3-year probability of OS and EFS was 33% and 29% respectively. In the univariate analysis we only found a trend to better survival for MPAL t(9;22) BCR-ABL1 WHO category (p = 0.11), ALL-based chemotherapy induction (p = 0.07), chemo-sensitiveness (p = 0.05) and allo-HSCT consolidation strategy (p= 0.09).

CONCLUSIONS

Our results are in consonance with the already known poor prognosis of this entity, in which the best induction approach correspond to ALL-based chemotherapy followed by allo-HSCT consolidation.
We observed that the WHO classification is less inclusive than the preceding EGIL system, resulting in a lower prevalence. There is no genetic alteration that can serve has hallmark lesion in MPAL, and Next Generation Sequencing (*NGS*) technology could refine the diagnosis and our understanding of this entity. We already planned to carry out *NGS* analysis in frozen bone marrow samples at diagnosis of our series.

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