Long-term follow up of intensively treated AML patients in the HARMONY Big Data Platform

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HARMONY ALLIANCE

AML

INTRODUCTION

Intensive therapy, based on anthracyclines and cytarabine, followed by allogeneic stem cell transplantation (alloHSCT) remained the backbone of AML treatment for decades.
In 2010 the European LeukemiaNet (ELN), based on cytogenetic and molecular genetic characteristics, proposed a risk score to facilitate decisions concerning indications for alloHSCT. Due to constant improvement in understanding the complex biology of acute myeloid leukemia (AML), in 2017 a new era of targeted AML therapy began. Nevertheless, the outcome of AML patients is still unsatisfactory with the 5-year OS around 30% (ref1).

AIM

To analyze changes in epidemiology, management and outcome of AML patients intensively treated between 1997 and 2016 (prior to the era of targeted therapy).

METHOD

Quality controlled, Observational Medical Outcomes Partnership (OMOP), Common Data Model (CDM), harmonized data of the HARMONY Alliance database coming from 100 organizations in 18 European countries were used for this study. Out of all AML records, 5359 patients were selected. The **inclusion criteria** were as follows: 1. AML treated with intensive chemotherapy (Ara-C at minimal dose of 100-200 mg/m2/d × 5-7 days). 2. Diagnosis and therapy between 1997-2016. Patients treated with intensive regimens were identified regardless of age by the type of chemotherapy (n=4287) or by the age ≤70 (n=1072) if there was no clear information concerning the therapy. Patients with acute promyelocytic leukemia and those treated with supportive care (SC), hypomethylating agents or targeted therapy were excluded from the analysis. Patients were categorized into 4 calendar periods: 1997-2001 (gr1), 2002-2006 (gr2), 2007-2011 (gr3) and 2012-2016 (gr4). The main outcome parameters analyzed were patient characteristics, overall survival (OS) and relapse-free survival (RFS). OS and RFS were determined using Kaplan-Meier analysis.

RESULTS

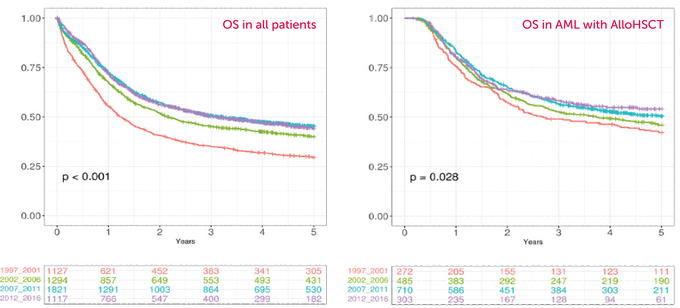
Patients

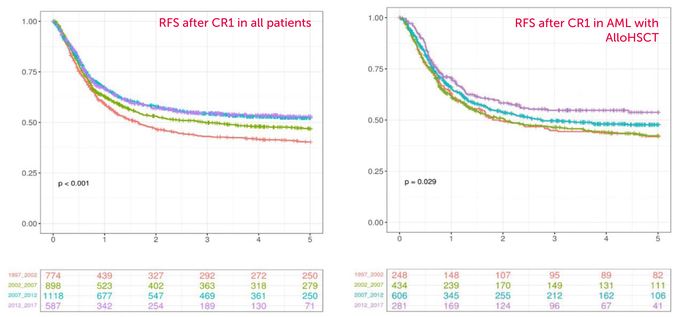
Characteristics	Total n=5359	Group 1 (1997-2001) n=1127	Group 2 (2002-2006) n=1294	Group 3 (2007-2011) n=1821	Group 4 (2012-2016) n=1117	p
Age, media (range), y < 60, n (%) 60-69, n (%) ≥ 70, n (%)	53 (18-85) 3745 (69.8) 1229 (22.9) 385 (7.18)	55 (17-84) 689 (61.1) 307 (27.2) 131 (11.6)	51 (15-85) 1012 (78.2) 206 (16) 76 (5.8)	53 (16-86) 1312 (72) 403 (22.1) 106 (5.9)	55 (17-85) 732 (65.5) 313 (28) 72 (6.5)	< 0.001
Female sex, n (%)	2498 (46.6)	509 (45.2)	620 (47.9)	853 (46.8)	516 (46.2)	0.5835
ECOG 0-1, n (%)	2325 (78.3)	660 (70.3)	835 (81.4)	671 (84.7)	159 (75)	< 0.001
WBC, median (IQR) (x10^6/mL)	16000 [Q1=4500-Q3=49900] [N=4356]	18320 [Q1=4900-Q3=53975] [N=1122]	18755 [Q1=5300-Q3=55950] [N=1154]	14930 [Q1=4300-Q3=46000] [N=1368]	12250 [Q1=3685-Q3=35000] [N=712]	< 0.001
Bone marrow blasts, %, median (IQR)	70 [Q1=46,5-Q3=85] [N=3552]	70 [Q1=48,5-Q3=85] [N=1040]	75 [Q1=48-Q3=90] [N=1096]	70 [Q1=46-Q3=85] [N=1067]	63 [Q1=40-Q3=80] [N=349]	< 0.001
Intensive regimens <70 years, n (%) **≥70 years, n (%)**	4974 (92.82) **385 (7.18)**	996 (88.4) **131 (11.6)**	1218 (94.2) **76 (5.8)**	1715 (94.1) **106 (5.9)**	1045 (93.5) **72 (6.5)**	< 0.001
HCT in CR1, yes (n,%)	1770 (33)	272 (24.1)	485 (37.5)	710 (39)	303 (27)	< 0.001
Median follow-up, months (range)	23.5 (0-213.1)	14.5 (0-213)	23.4 (0-145.1)	24.4 (0-196.8)	31.5 (0-161.6)	-

Early mortality

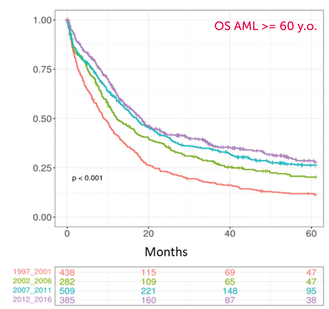
Characteristics	Total n=5359	Group 1 (1997-2001) n=1127	Group 2 (2002-2006) n=1294	Group 3 (2007-2011) n=1821	Group 4 (2012-2016) n=1117
Early death					
≤ 2 wk	96 (1.79%)	34 **(3.01%)**	22 (1.7%)	31 (2.7%)	9 **(0.81%)**
4 wk	232 (4.33%)	71 **(6.3%)**	57 (4.4%)	76 (4.17%)	28 **(2.5%)**
8 wk	435 (8.12%)	147 **(13.04%)**	105 (8.11%)	130 (7.14%)	53 **(4.74%)**

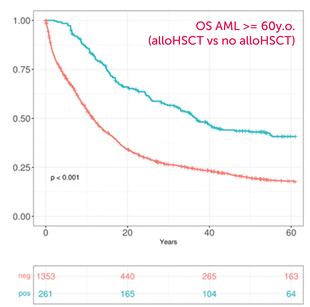
AlloHSCT improves OS and RFS rate across all 4 calendar periods



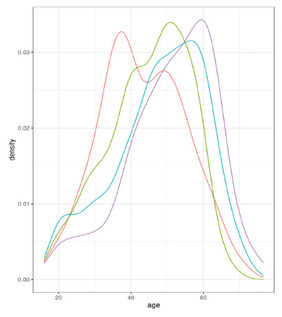


Patients >60 years profit from intensive therapy and alloHSCT





OS - shifting in age when alloHSCT is performed



	1997 – 2001	2002 - 2006	2007 - 2011	2012 - 2016
Median Age	42	47	50	53

The median age to perform alloHSCT (p=0.028):
Gr1: 42.1 (18 - 71) years
Gr2: 46.9 (16 - 69) years
Gr3: 49.9 (17 - 75) years
Gr4: 53 (18 - 77) years

CONCLUSIONS

This is a first long-term historical study performed only on AML patients intensively treated (ref. 2-4). Overall Survival of intensively treated AML patients steadily improved over a long-term follow up of large historical (1997-2016) cohorts due to several factors:

- The rate of early deaths decreased over the observation period, most likely related to improved supportive care.
- AlloHSCT improved OS and RFS rate across all 4 calendar periods.
- OS of patients >= 60 years with alloHSCT strongly improved.
- Improvement of OS was paralleled by performing alloHSCT at more advanced age.

Next steps: deciphering the impact of genetic differences across calendar periods.

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The HARMONY Alliance is a Public-Private Partnership for Big Data in Hematology including over 100 organizations such as European medical associations, hospitals, research institutes, patient organizations, pharmaceutical and IT companies.

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