Outcomes with intensive treatment for acute myeloid leukemia: an analysis of two decades of data from the HARMONY Alliance

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Supplemental Data to

Outcomes with intensive treatment for acute myeloid leukemia over two decades: An analysis from the HARMONY Alliance.

Running title: Intensive treatment for acute myeloid leukemia over two decades.

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Supplemental Methods

Therapy

Intensive induction regimen was defined based on the use of cytarabine (Ara-C) at 100-200 mg/m² daily over 5-7 days. Induction therapy varied by treatment period and local protocols. Variations in these regimens included different anthracyclines (daunorubicin, idarubicin, mitoxantrone), the addition of other types of chemotherapy, such as thioguanine, etoposide, nucleoside analogues (fludarabine, clofarabine, cladribine), or differentiating agents such as valproate, tretinoin plus valproate, with or without granulocyte colony-stimulating-factor. Patients receiving non-cytarabine based regimens, and those treated with epigenetic (hypomethylating) or targeted therapy (anti CD-33 or genetically targeted) were excluded from the analysis. Response to therapy was defined according to the Cheson[29] and ELN criteria[6]. Early death was defined as the death within 14, 30 and 60 days from diagnosis. Patients receiving consolidating allogeneic hematopoietic cell transplantation (alloHCT) were included independent of alloHCT type, including grafts from related or unrelated donors without and with HLA mismatch. The remission status at alloHCT was CR1 for the majority of patients. Myeloablative and reduced intensity conditioning regimens were permitted.

Outcomes and Statistical analysis

The main clinical outcome parameters were overall survival (OS) and relapse-free survival (RFS) as determined by Kaplan-Meier analysis. The observation period was 5 years. The OS was calculated from the date of AML diagnosis to death from any cause, censoring patients who were alive at the time of last follow up. The RFS was calculated for patients achieving complete remission (CR) measured from the date of achievement of remission until the date of hematologic relapse or death from any cause, censoring patients who were not known to have relapsed or who were alive at last follow-up. In addition, relapse and death were considered as competing events and were analyzed by competing risk analysis. Cumulative incidences were compared by Gray's test. P-values <0.05 were considered statistically significant. Both OS and RFS (primary endpoints) were compared between the four treatment periods using the log-rank test. Associations between patients' features and time-to-event endpoints (OS, RFS) were determined by multivariable Cox regression analysis[24]. Several multivariable Cox regression models including 5359 patients (10 covariates), 4356 (11 covariates) and 3439 patients (12 covariates) were constructed and compared using the Akaike information criterion[25]. All covariates entered the first model. Variables were selected

by retaining significant variables in univariate Cox analysis and clinically relevant variables for the multivariate models. The strongest OS model was retained as final and is displayed in the results (Figure 5). The following covariates entered multivariate analysis: age, gender, ELN risk, calendar treatment period of 5 years each (1997-2001, 2002-2006, 2007-2011, 2012-2016), ECOG performance index, logarithm (log) of white blood cell (WBC) counts, hemoglobin and platelet levels, the percentage of bone marrow blasts at diagnosis and the performance of alloHCT. AlloHCT was analyzed as time-dependent co-variate in Cox-regression analysis. For the direct head-to-head comparison of patients aged 60 years and older with and without alloHCT using Kaplan Meier survival analysis we employed the landmark analysis as previously described[30]. The median time from diagnosis to alloHCT was 143 days, the landmark was also set at 143 days. Patients in both groups that died or were censored before that date were not considered in this analysis.

Calculations were performed with *R*[36] (version 4.1.3, R Core team 2020, https://www.r-project.org) using the following libraries: *ggplot2, surviva*[37]*, survminer*[38]*, cmprsk*[39].

Supplemental Tables

Supplemental Table 1. List of chemotherapy regimens (n=4286).

Induction chemotherapy	***n* (%)**
DNR/IDA + Ara-C	1227 (28.7%)
DNR/IDA + Ara-C + Miscellaneous	2265 (52.9%)
Mitoxantrone + Ara-C	409 (9.5%)
Mitoxantrone + Ara-C + Miscellaneous	380 (8.8%)
HD Ara-C	5 (0.1%)

Abbreviations: Ara-C, cytarabine, DNR, daunorubicin; and IDA, idarubicin.

Supplemental Table 2. Comparison of baseline characteristics between all patients and separate for those with documented intensive chemotherapy regimen and for those aged <70 years.

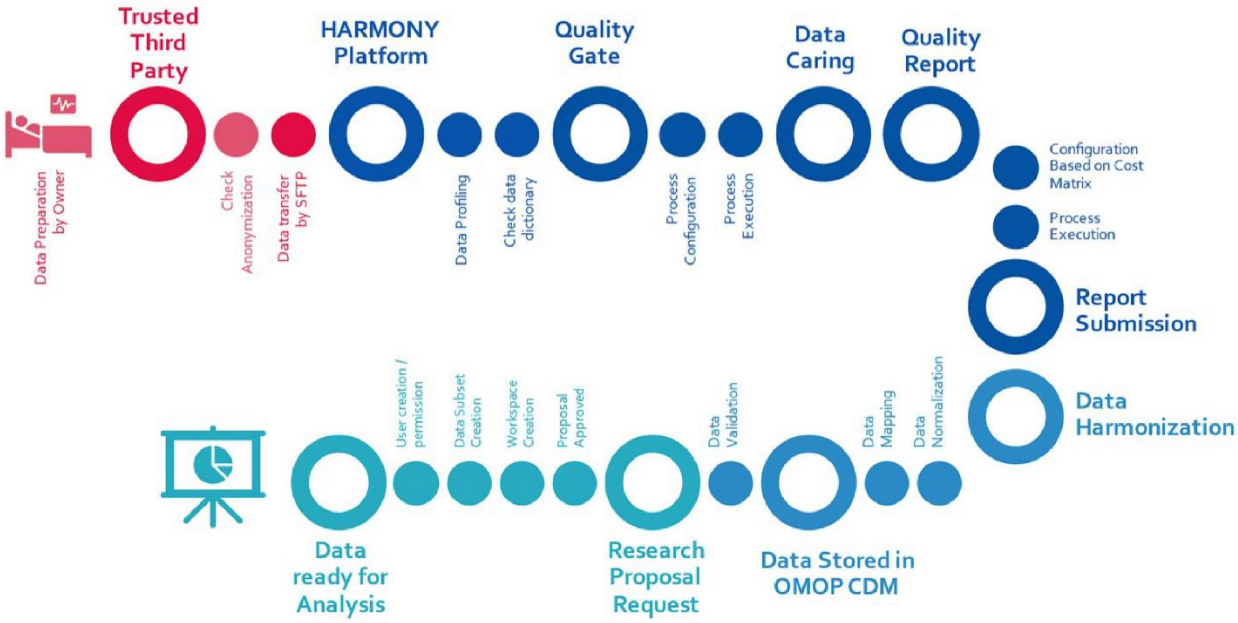
Characteristics	Total (n=5359)	With detailed chemotherapy (n=4287)	Patients ≤70 (n=1072)	*p*
Age, median (range)	53 (18-85)	53 (18-85)	54 (18-70)	0.6796
Female sex, n (%)	2498 (46.6)	1995 (46.5)	503 (46.9)	0.8476
ECOG 0-1, n (%) (n = 2934)	2325 (78.3)	2293 (79.1)	32 (91.4)	0.1144
ELN 2017 favorable intermediate adverse	 1790 1977 1592	 1631 (38%) 1257 (29%) 1399 (33%)	 159 (15%) 720 (67%) 193 (18%)	< 0.01
Hb, median (range) g/dl n=2598	9 (2.5-19)	9 (2.5-19)	9 (3.4-15.4)	0.7593
WBC, median (IQR) (x10^6/mL) n=4356	16000 [Q1=4,500-Q3=49,900]	16200 [Q1 = 4,500 – Q3 = 50,867.5]	12100 [Q1 = 4,850 – Q3 = 31,450]	0.07322
Platelets, median (IQR) (x10^6/mL) n=4171	53000 (Q1=29,000 – Q3=100,000)	53000 (Q1=29,000 – Q3=100,000)	49000 (Q1=26,000 - Q3=98,000)	0.3051
Bone marrow blasts, %, median (IQR) n=3552	70 [Q1=46.5 - Q3=85]	70 [Q1=47 - Q3=85]	63 [Q1=40 - Q3=82.5]	0.02271

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance index; IQR, interquartile range; Q, quartile; ELN, European LeukemiaNet; Hb, hemoglobin; WBC, white blood cells.

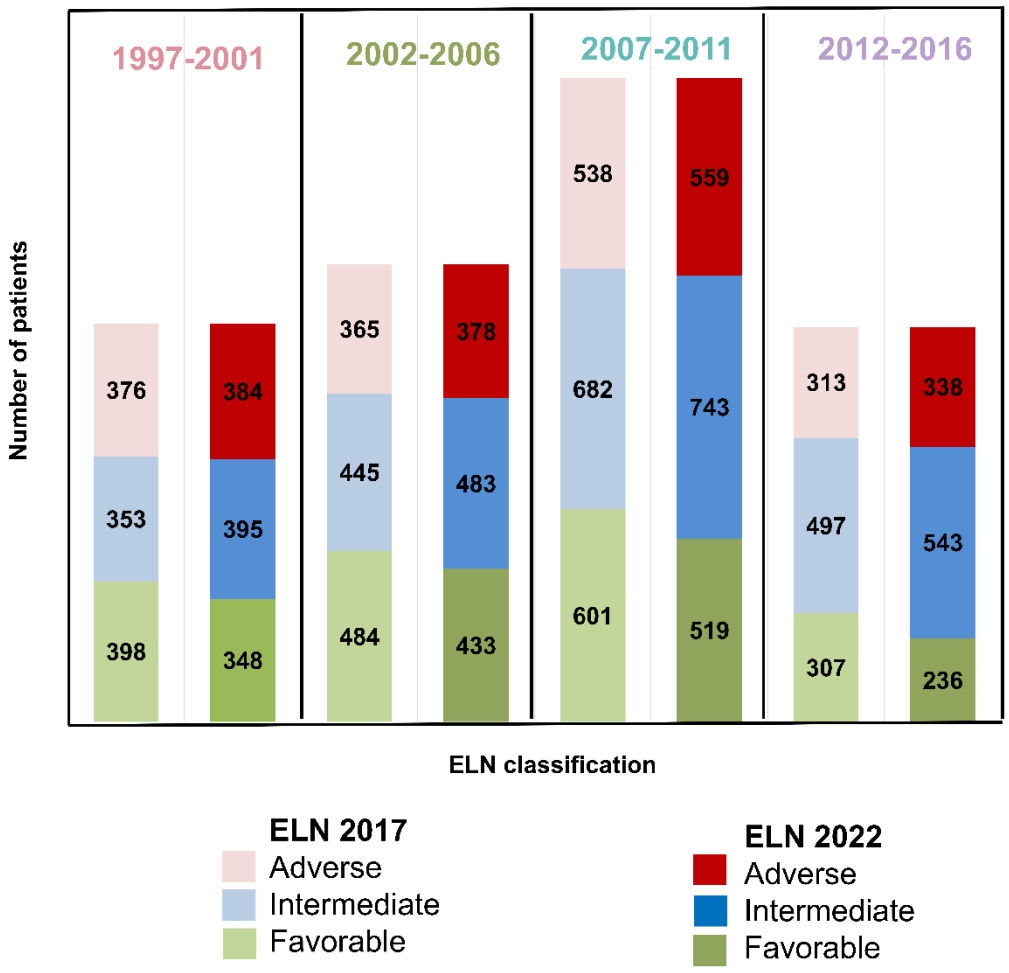
Supplemental Figures

Supplemental Figure 1. Data anonymization and harmonization process.

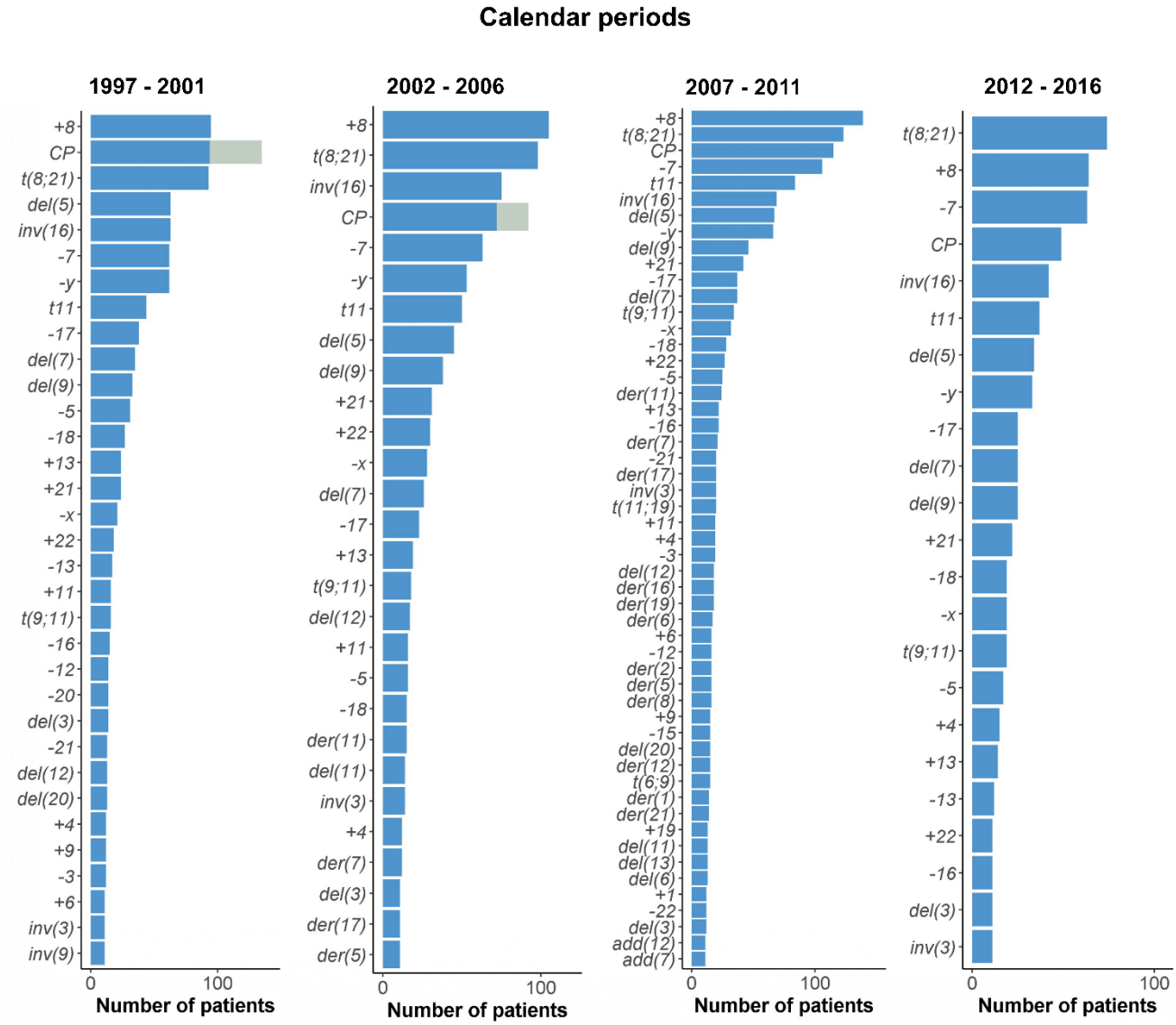
Data providers share de-identified datasets with the trusted third party (TTP). TTP provides second pseudonymization (unknown to the data provider) and transfers the data to the HARMONY platform. Quality gating evaluates and maps the data dictionary with the provided data. Quality report is provided before further data processing. Research proposals for the data in HARMONY are submitted to and evaluated by the Harmony steering committee. Only de-identified data from the HARMONY database is provided for researchers on a need-to-know basis.



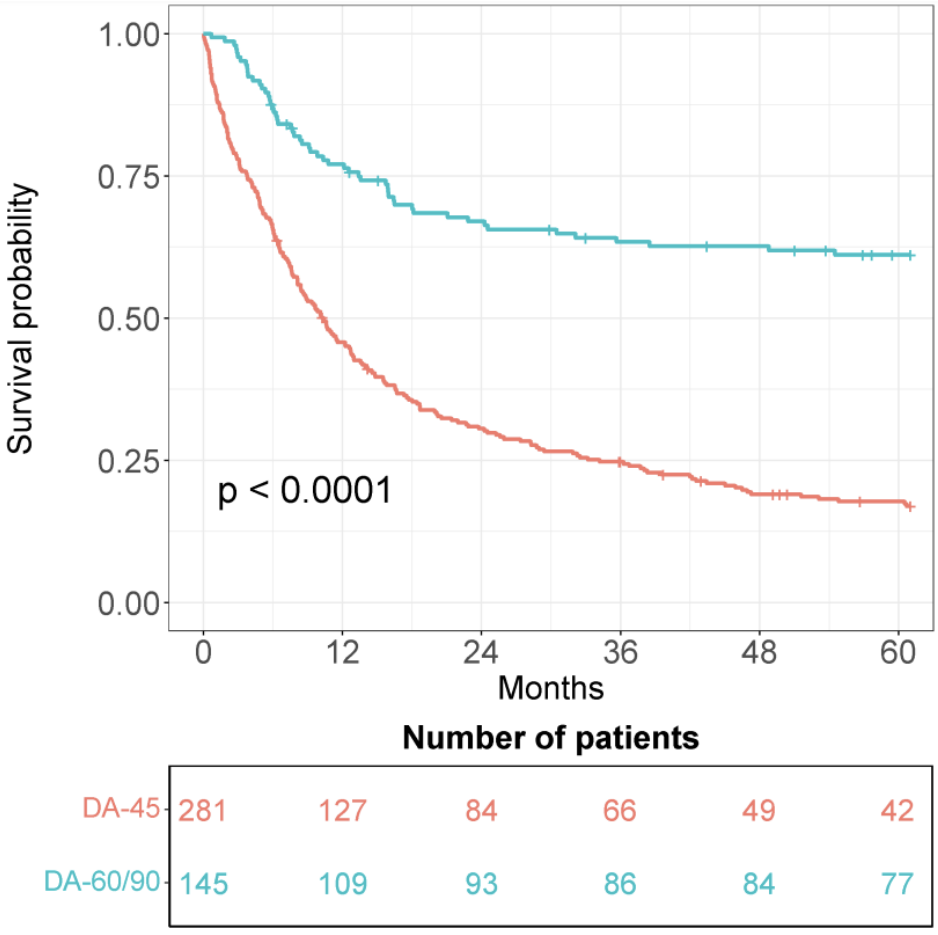
Supplemental Figure 2. Proportion of patients according to ELN 2017 and ELN 2022 for each calendar period.



Supplemental Figure 3. Stable proportion of main cytogenetic abnormalities across four calendar periods.



Supplemental Figure 4. Impact of doses of daunorubicin on overall survival of AML patients.



Supplemental Figure 5. Comparison of OS in patients aged ≥70 years (n=385).

A Comparison of OS across 4 calendar periods, **B** Comparison of OS in patients ≥70 years with alloHCT (n=21, blue) and without alloHCT (n=364, red)