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RESEARCH

# Trends in acute myeloid leukaemia in Western Australia over time: Improved outcomes with contemporary management

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**Abstract**

**Introduction:** Real-world survival in acute myeloid leukaemia (AML) is poor, and there has been little change to the intensive induction and consolidative chemotherapy regimens over 30 years. Despite this, there have been developments in therapeutic agents for patients unfit for intensive therapy, supportive care, risk stratification and allogenic stem cell transplant. We report outcomes of these patients with AML treated using contemporary care standards in Western Australia (WA) and compare this with a historical cohort.

**Methods:** AML diagnosed between 2009-2018 in WA were identified by discharge diagnosis at 3 tertiary public hospitals in Perth and the database of the state reference cytogenetic laboratory at Pathwest. Medical and laboratory records were reviewed retrospectively for characteristics and outcomes. Comparison was made with a historical cohort diagnosed 1991-2015 and analysed with t-test and Kaplan-Meier methods.

**Results:** 734 patients were identified in the contemporary period. Median age was 64.4 years and 70% were primary/*de novo* AML. 61% were managed with intensive chemotherapy and 16.9% of these under the age of 60 proceeded to allogeneic stem cell transplant in first remission. There were no significant differences in the rates of intensive therapy or allogenic transplantation compared with the historical cohort. 98.8% of patients had successful cytogenetic studies performed. Of those with a normal karyotype, molecular studies were performed in 57%. Median overall survival in patients treated intensively was 56.6 months for age 60 or less, and 10 months in patients age over 60. Cytogenetic risk group predicted survival ($p<0.0001$). Survival was significantly improved in both groups treated intensively and non-intensively compared with the historical cohort; 18.7 vs 13.2 months (HR 1.348, 95% CI 1.157-1.571) and 3.1 vs 1.6 months (HR 1.431, 95% CI 1.1223-1.674) respectively.

**Conclusion:** Survival has improved in all patients with AML in WA over time despite no significant change to intensive chemotherapy regimens. This may be explained by improved risk stratification, supportive care, non-intensive therapy options, and allogeneic donor selection and transplantation techniques.

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## Introduction

Real-world outcomes of acute myeloid leukaemia (AML) are poor compared to the results of clinical trials. This partially reflects population differences due to patient selection criteria in trials (excluding older and unfit patients who are unsuitable for aggressive treatment), and lack of improvement in the efficacy of intensive chemotherapy over time. However, there have been successful developments in AML management including improved non-intensive

therapies, laboratory diagnostics to stratify patient risk, donor selection for allogeneic stem cell transplantation (allo-SCT) and supportive care. We have performed a retrospective analysis of all cases of AML in Western Australia from 2009 to 2018 with respect to clinical and laboratory characteristics, treatments and outcomes, compared to a historical cohort.

**Methods**

AML was defined as per the 2016 WHO classification[1]. Cases were identified by hospital discharge summary records at 3 tertiary public hospitals in WA and the laboratory cytogenetics records for new diagnoses of AML between 2009 and 2018 in patients aged 16 years or older. Medical records were reviewed for clinical data and correlated with cytogenetic and molecular data from Pathwest laboratory. Cytogenetic and molecular risk stratification was defined according to 2017 European LeukemiaNet guidelines[2]. Intensive chemotherapy regimens were defined as those delivered with curative intent including 7+3 and FLAG. Non-intensive therapy was defined as chemotherapy unlikely to result in prolonged remission, such as subcutaneous azacytidine and cytarabine. These results were compared with a cohort of AML patients in WA diagnosed between 1991-2005, previously published[3] which used the modified Grimwade criteria for cytogenetic classification[4].

GraphPad Prism version 8 for macOS was used for statistical analysis. Unpaired t-test, Mann-Whitney test and Fisher's exact test was used to compare populations of AML patients. Kaplan-Meier method was used to calculate overall survival (OS) and logrank analysis was used to compare survival curves.

This research project was approved by the South Metropolitan Health Service Human Research Ethics Committee.

| | Current (2009-2018) | Historical (1991-2005) |
|---|---|---|
| Sex | | |
| Male | 418 (56.9%) | 505 (56.4%) |
| Female | 316 (43.0%) | 391 (43.6%) |
| Age | | |
| Median | 64.4 years | 66.6 years |
| Range | 16-94 years | 16-94 |
| Predisposing disorder | | |
| *De novo* AML | 513 (70.0%) | 494 (58%) |
| Secondary AML | 220 (30%) | 358 (42%) |
| -MDS | 133 (18%) | 226 (26.5%) |
| -chemotherapy related | 63 (8.6%) | 70 (7.3%) |
| -MPN | 24 (3.3%) | 62 (8.2%) |

Table 1. Demographic details. MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm

**Results**

734 diagnosis of AML were identified between 2009-2018. Demographic details are presented in Table 1. A greater proportion of patients were male, and 446 (60.8%) were over the age of 60 years. Secondary AML was present in 220 patients and the most common predisposing factor was myelodysplastic syndrome in 133 (60%). Cytogenetic studies were available in 710 (96.8%) patients and in 98.9% of patients treated intensively. Cytogenetic risk groups are presented in Table 2A and 2B.

Table 2A

| Subgroups | Total number with evaluable cyto-genetics | Cytogenetic classification by percentage of total | | |
|---|---|---|---|---|
| | | Fav-ourable | Inter-mediate | Adverse |
| All patients | 710 | 13% | 51% | 36% |
| Intensive therapy | 442 | 20% | 50% | 30% |
| Age 60 or less | 286 | 22% | 50% | 28% |
| Age >60 years | 424 | 7% | 52% | 41% |
| *De novo* AML | 503 | 18% | 53% | 29% |
| Secondary AML | 206 | 1% | 45% | 53% |

Table 2B

| Subgroups | Total number with evaluable cyto-genetics | Cytogenetic classification by percentage of total | | |
|---|---|---|---|---|
| | | Favour-able | Inter-mediate | Adverse |
| All patients | 726 | 14% | 64% | 22% |
| Intensive therapy | 458 | 19% | 64% | 17% |
| Age 60 or less | 294 | 27% | 57% | 16% |
| Age >60 years | 403 | 5% | 68% | 27% |
| *De novo* AML | 420 | 21% | 63% | 16% |
| Secondary AML | 273 | 5% | 65% | 30% |

Tables 2A and 2B. 2A shows current cohort cytogenetic risk groups by therapy and risk factors using the ELN 2017 classification;[2] 2B shows the historical cohort by the classification of Grimwade *et al* (2010).[4]

Rates of specific cytogenetic abnormalities are shown in Table 3. Most patients were of intermediate risk regardless of age, secondary disease or type of therapy. The rate of adverse cytogenetics was greater in older patients, and in patients with secondary AML. For patients with a normal karyotype (n = 284), molecular studies for *FLT3* (*FLT3-TKD* and *FLT3-ITD*) and

*Nucleophosmin* (*NPM1*) mutations were performed in 57%, and in 73% of patients managed with intensive therapy. Results of molecular studies for mutations are presented in Table 4.

A summary of therapy is present in Table 5. Median age of patients who received intensive therapy was 56 years (range 16-89). 48 of these patients received an allo-SCT as primary therapy. Median age in this group was 47 years (range 16-65). Median time to allo-SCT from diagnosis was 189 days (range 28-565). Of patients who received non-intensive therapy, 87 (30%) received a hypomethylating agent and 52 (18%) received an alternative cytotoxic agent including subcutaneous cytarabine, hydroxycarbamide and clinical trial agent.

| Cytogenetic abnormality | n | % |
|---|---|---|
| Normal | 285 | 38.8 |
| Complex | 151 | 20.6 |
| *t*(15;17) | 57 | 7.8 |
| +8 | 42 | 5.7 |
| t(v;11) | 26 | 3.5 |
| -7 | 26 | 3.5 |
| *t*(8;21) | 23 | 3.1 |
| Inv(16) | 14 | 1.9 |
| -9 | 6 | 0.8 |
| +21 | 5 | 0.7 |
| Inv(3) | 5 | 0.7 |
| -Y | 4 | 0.5 |
| -5 | 4 | 0.5 |
| +4 | 4 | 0.5 |
| *t*(9;22) | 1 | 0.1 |
| Other with 2 or more unrelated chromosomal abnormalities | 7 | 1.0 |
| Other low frequency abnormalities | 40 | 5.4 |
| unknown | 34 | 4.6 |

Table 3. Rates of cytogenetic abnormalities. 'Complex' = 3 or more unrelated chromosome abnormalities.

| | Number |
|---|---|
| Molecular results available | 162 |
| *NPM1* pos, *FLT3* neg | 42 (26%) |
| *NPM1* pos, *FLT3* pos | 38 (23%) |
| *NPM1* neg, *FLT3* neg | 62 (38%) |
| *NPM1* neg, *FLT3* pos | 20 (12%) |

Table 4. Molecular studies performed in normal karyotype AML. *NPM1*, *Nucleophosmin* mutation; *FLT3*, *FLT3-ITD* or *FLT3-TKD* mutation

The proportion of patients managed intensively was not significantly different (61% vs 58%, p=0.2607) from the corresponding datum in the 1991-2005 cohort. There was no significant difference of the age of patients managed intensively (mean 55 vs 54 years, p=0.51). For patients 60 years old or younger, there was no difference in rates of allo-SCT in first remission compared with the 1991-2005 cohort (16.9% vs 14.3%, p=0.41). The mean age of patients undergoing primary allo-SCT in the current cohort was significantly older than before (45 vs 39 years, p=0.0245). Time from diagnosis to allo-SCT was longer in the contemporary cohort; median 189 vs 125 days (p=0.0011).

| | Number Age ≤60 | Number Age >60 |
|---|---|---|
| Intensive chemotherapy alone | 216 | 183 |
| Intensive chemotherapy and Allo-SCT in CR1 | 44 | 4 |
| Non-intensive therapy | 28 | 259 |

Table 5. AML therapy by age. CR1, first complete remission

Overall median survival from diagnosis in the current populations was 10.3 months. For patients treated intensively, median OS was 56.6 and 10 months according to age (≤ 60 and > 60 y, respectively). Cytogenetic stratification predicted OS (Figure 1). Patients who received allo-SCT as primary therapy had improved OS compared with patients who received intensive chemotherapy alone (Figure 2).

When compared to the 1991-2005 cohort, OS in patients managed both intensively and non-intensively was significantly improved (Figure 3 and 4). There was no significant difference in median survival of patients undergoing primary allo-SCT between the historical (108.5 m) and current cohort (not reached) (HR 1.075, 95% CI 0.5785 to 1.998) (not shown).

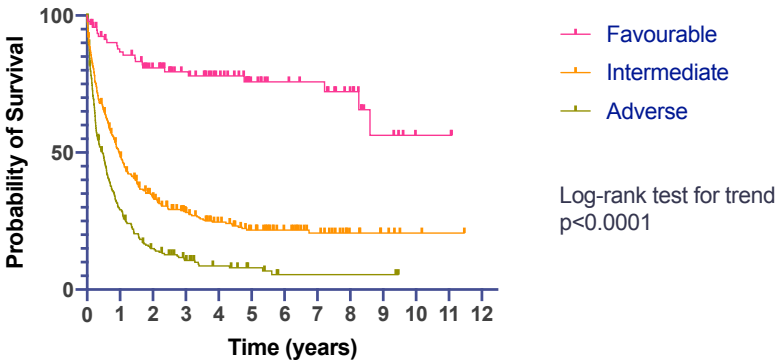


Figure 1. Kaplan-Meier curve for OS by cytogenetic risk group

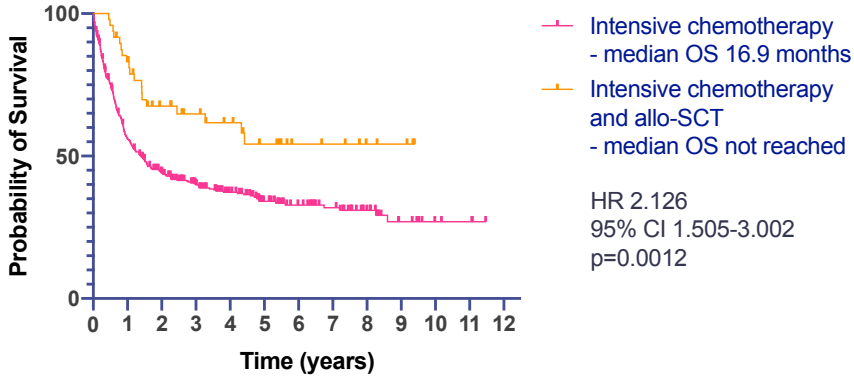


Figure 2. Kaplan-Meier curve for OS in intensive chemotherapy alone vs intensive chemotherapy followed by allo-SCT

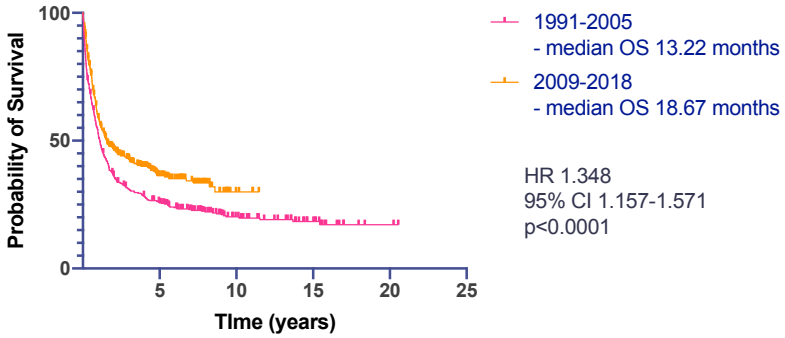


Figure 3. Kaplan-Meier curve for OS in patients receiving intensive chemotherapy (including allo-SCT in CR1), 1991-2005 vs 2009-2018 cohort.

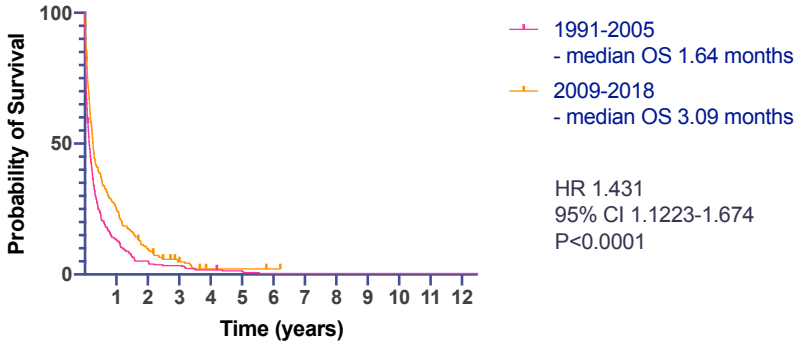


Figure 4. Kaplan-Meier curve for OS in non-intensively managed patients, 1991-2005 vs 2009-2018 cohort.

**Discussion**

The current cohort of AML treated between 2009-2018 has improved survival compared with treatment during 1991-2005 for both intensively and non-intensively managed patients. The improvement in non-intensively treated patients may be due to newer therapeutic options such as hypomethylating agents[5] or subcutaneous cytarabine-based treatments[6, 7] which demonstrate favourable response rates in a group of patients with historically poor outcome. In addition, improved supportive care became available including anti-fungal treatments such as posaconazole which may reduce the morbidity and mortality associated with infections due to prolonged neutropenia from disease or therapy[8].

The superior survival for patients managed with intensive chemotherapy may also reflect improved supportive care. However the chemotherapy regimens remain similar to that of the 1991-2015 era, consisting of a backbone of intravenous cytarabine and anthracycline-based chemotherapy. Modifications of these agents have failed to demonstrate improvement in survival in clinical trials[9, 10].

Better patient selection for intensive management and primary allo-SCT could partially explain the improved survival in this group. High rates of cytogenetic and molecular testing was noted, which is required for accurate risk stratification according to modern European LeukemiaNet[2] guidelines to help identify high-risk patients which may benefit from primary allo-SCT. The higher rates of adverse cytogenetics observed in the current cohort compared with the historical cohort are likely to reflect the differing classification systems used for decision-making at the time. Despite this, rates of primary allo-SCT were similar to that of the historic cohort, and outcomes of these patients were similar. Other confounding factors such as increased age at allo-SCT and alternative donor availability with non-related and mismatched donors could influence survival from allo-SCT while in first remission[11]. This is supported by the relative long lead time from diagnosis to transplant, which may reflect the donor search.

Improvement in survival for AML patients over time is promising, however this appears unrelated to improvements in induction or consolidative chemotherapy, as these regimens have not changed significantly. Advancements in risk stratification, allogeneic transplant and supportive care are likely to account for the modest but significant increased OS in these patients. Overall outcomes remain poor and development of chemotherapy agents with improved efficacy is required. Emerging novel agents such as FLT3 inhibitors, liposomal cytarabine, venetoclax and IDH inhibitors demonstrate promise for AML in specific groups[12-17]. Some of these are currently being incorporated into contemporary AML care. Pursing these agents in practice and identifying the patients who benefit is likely to improve outcomes for future patients with AML.

**Provenence:** Externally reviewed
**Ethics:** Approval obtained.
**Disclosures:** None

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