PO-014

Analysis of treatment patterns and outcomes for patients with therapy-related acute myeloid leukaemia and acute myeloid leukaemia with myelodysplasia-related changes diagnosed in England between 2011–2016 using Hospital Episode Statistics®

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Background

- Two subgroups of the World Health Organisation 2016 diagnostic criteria for acute myeloid leukaemia (AML) include therapy-related AML (t-AML) and AML with myelodysplasia-related changes (AML-MRC)[1]
  - Patients with t-AML have received prior chemotherapy or radiotherapy
  - AML-MRC is defined as: 1) history of myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm, 2) MDS-related cytogenetic abnormality, or 3) multilineage dysplasia (MLD) in >50% of ≥2 cell lineages in the absence of *NPM1* or biallelic *CEBPA* mutations
- Historically, patients with t-AML or AML-MRC have lower remission rates and shorter overall survival (OS) with conventional intensive chemotherapy (IC) compared with those with *de novo* AML[2,3]
- Alternative, less intensive therapies for AML include hypomethylating agents (eg, azacitidine) and low-dose cytarabine (LDAC)
  - Azacitidine is approved in Europe for adults with AML who are not eligible for haematopoietic stem cell transplantation (HCT).[4] The National Institute for Health and Care Excellence (NICE) recommends azacitidine for low–blast count AML with MLD (20% to 30% bone marrow blasts) but not AML with >30% blasts[5,6]
  - In a retrospective analysis of 17 years' worth of experience with LDAC in AML patients not fit for intensive treatment, the median response rate (complete response or complete response with incomplete haematological recovery) was 19%, with a median OS of 160 days and a 60-day mortality rate of 28%[7]
- A comparison of treatment patterns and outcomes among patients with t-AML, AML-MRC, and *de novo* AML in recent years in England is lacking in the published literature

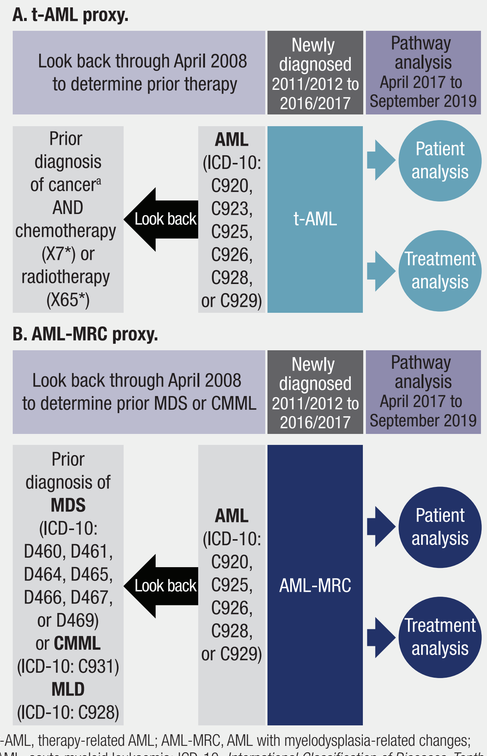
Objective

- To perform a retrospective study using the Hospital Episode Statistics© (HES) database to describe the historical treatment patterns in England (2011–2016) and analyse long-term outcomes for patients with t-AML, AML-MRC, or *de novo* AML
- The timeframe of this analysis (2011–2016) is prior to European Medicines Agency approval of any agents specific for t-AML or AML-MRC (eg, CPX-351)

Methods

- HES is a National Health Service (NHS) database containing details of all admissions, accident and emergency attendances, and outpatient appointments at NHS hospitals in England
- Adult patients (≥18 years old) who were diagnosed with AML between NHS years (April–March) 2011/2012 to 2016/2017 were identified through *International Classification of Diseases, Tenth Revision* (ICD-10) diagnosis codes (C92*, excluding C921, C922, and C927)
  - There are no ICD-10 codes specific to t-AML or AML-MRC, and these patients were identified through a history of a relevant cancer and specific OPCS-4 procedure codes for chemotherapy (X7*) or radiotherapy (X65*), a history of MDS (ICD-10: D46*) or chronic myelomonocytic leukaemia (CMML; ICD-10: C931), or a diagnosis of AML with MLD (ICD-10: C928)
  - To avoid counting a patient multiple times, the following diagnostic hierarchy was applied: t-AML > prior MDS or CMML > AML with MLD
  - Patients with AML who did not fall into these criteria were classified as *de novo* AML
  - Based on chemotherapy and transplant OPCS-4 codes, patients were allocated to the following AML treatment pathways: IC ± HCT, azacitidine ± HCT, or LDAC
- Patients who did not receive active systemic therapy (ie, best supportive care alone) were excluded
- Median patient follow-up was 5.3 years (100% range: 2.5, 8.8)

Figure 1. t-AML and AML-MRC proxy diagrams.



t-AML, therapy-related AML; AML-MRC, AML with myelodysplasia-related changes; AML, acute myeloid leukaemia; ICD-10, *International Classification of Diseases, Tenth Revision*; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukaemia; MLD, multilineage dysplasia.
[a]Previous diagnosis of cancer based on a selected list of cancer diagnoses.

Results

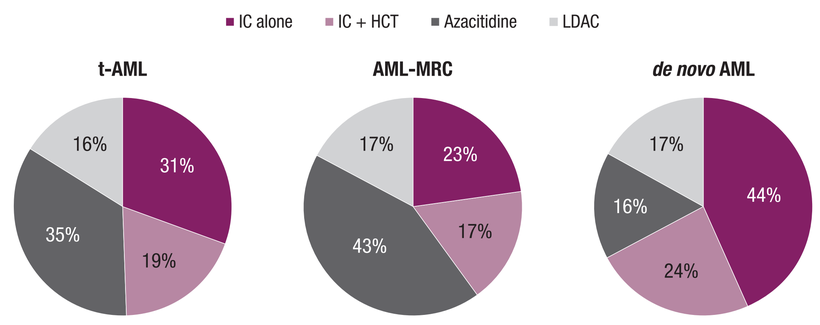
Table 1. Patient baseline characteristics.

Characteristic	t-AML or AML-MRC: All t-AML or AML-MRC n=2293	t-AML or AML-MRC: t-AML alone n=803	t-AML or AML-MRC: AML-MRC alone n=1490	*de novo* AML n=7465
Age, years				
Mean age	66	63	68	59
Median age (IQR)	69 (61, 75)	67 (56, 73)	69 (63, 76)	63 (50, 72)
<60, n (%)	522 (23)	264 (33)	258 (17)	3122 (42)
60 to 70, n (%)	808 (35)	260 (32)	548 (37)	2273 (30)
>70, n (%)	963 (42)	279 (35)	684 (46)	2070 (28)
Male, n (%)	1432 (62)	463 (58)	969 (65)	4208 (56)

t-AML, therapy-related AML; AML-MRC, AML with myelodysplasia-related changes; AML, acute myeloid leukaemia; IQR, interquartile range.

- Overall, 9758 patients with AML were identified, comprising 2293 (23%) patients with t-AML or AML-MRC (prior MDS: n=1305; prior CMML: n=151; MLD: n=34) and 7465 (77%) with *de novo* AML
- Patients with t-AML or AML-MRC were typically older (median [interquartile range] age: 69 years [61, 75] vs 63 years [50, 72]) and had a higher proportion of males (62% vs 56%) versus patients with *de novo* AML

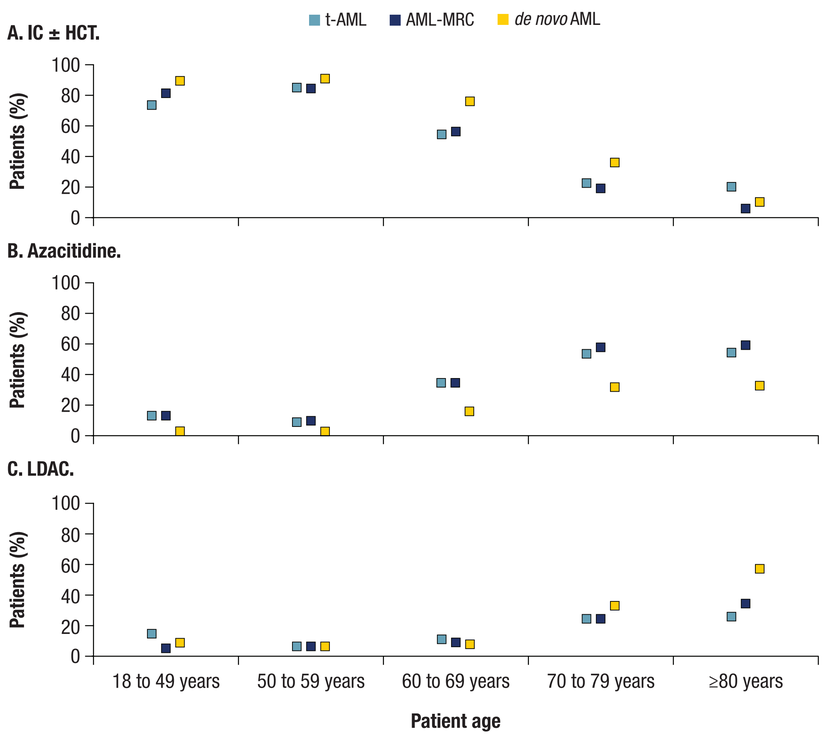
Figure 2. Treatments used for patients with t-AML, AML-MRC, and *de novo* AML.



t-AML, therapy-related AML; AML-MRC, AML with myelodysplasia-related changes; AML, acute myeloid leukaemia; IC, intensive chemotherapy; HCT, haematopoietic cell transplantation; LDAC, low-dose cytarabine.

- Patients with t-AML or AML-MRC were more likely to receive non-intensive azacitidine (40% vs 16%) and less likely to receive IC ± HCT (44% vs 68%) compared with those with *de novo* AML

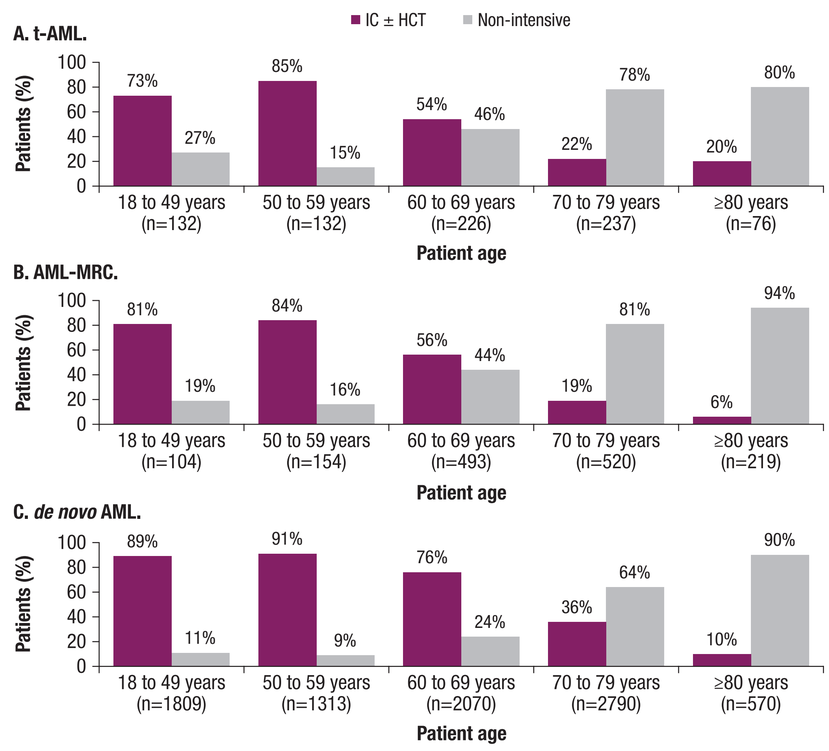
Figure 3. Impact of age on treatments used for patients with t-AML, AML-MRC, and *de novo* AML.



t-AML, therapy-related AML; AML-MRC, AML with myelodysplasia-related changes; AML, acute myeloid leukaemia; IC, intensive chemotherapy; HCT, haematopoietic cell transplantation; LDAC, low-dose cytarabine.

- To determine the impact of age on treatment choice, the use of IC ± HCT versus non-intensive azacitidine or LDAC was examined by age subgroups
  - The use of IC ± HCT was lower for patients with t-AML or AML-MRC versus those with *de novo* AML across most age deciles but most notably for patients aged 60 to 69 years and 70 to 79 years
  - The use of azacitidine was higher for patients with t-AML or AML-MRC versus those with *de novo* AML across all age deciles but most notably for patients aged 60 to 69 years, 70 to 79 years, and ≥80 years
  - Preferential use of LDAC was observed in patients aged 70 to 79 years and ≥80 years who had a diagnosis of *de novo* AML versus t-AML or AML-MRC

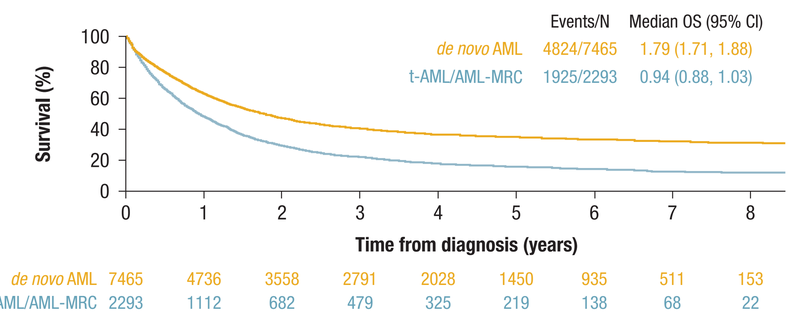
Figure 4. Impact of age on receipt of intensive (IC ± HCT) versus non-intensive (azacitidine or LDAC) treatment.



IC, intensive chemotherapy; HCT, haematopoietic cell transplantation; LDAC, low-dose cytarabine; t-AML, therapy-related AML; AML-MRC, AML with myelodysplasia-related changes; AML, acute myeloid leukaemia.

- The frequency of use of intensive and non-intensive therapies was roughly equivalent for patients with t-AML and AML-MRC in the 60- to 69-year-old age group; this balance shifted substantially for patients ≥70 years of age, whereby non-intensive therapies were used more than 4 times as frequently
- In contrast, for patients with *de novo* AML, only a quarter of patients aged 60 to 69 years received non-intensive therapy; the preference for non-intensive therapy in patients ≥70 years of age was also seen for *de novo* AML, but this was not as pronounced for the 70- to 79-year-old age group as with patients with t-AML or AML-MRC

Figure 5. Kaplan-Meier–estimated OS by AML subtype (all ages).



OS, overall survival; AML, acute myeloid leukaemia; CI, confidence interval; t-AML, therapy-related AML; AML-MRC, AML with myelodysplasia-related changes.

- The impact of AML subtype on OS was examined among patients with *de novo* AML versus those with t-AML or AML-MRC. Patients with *de novo* AML had significantly longer median OS versus t-AML or AML-MRC (median: 1.79 vs 0.94 years; unadjusted hazard ratio=1.66 [95% confidence interval: 1.58, 1.75]; nominal $P<0.0001$)

Strengths

- This analysis had a large sample size with nationwide coverage of data from England via the HES database
- Results could be linked to long-term OS data
- The median follow-up time was >5 years

Limitations

- Patient data for Eastern Cooperative Oncology Group performance status, minimal residual disease, relapse status, and remission rates were not available in the HES database
- Lack of cytogenetic data precluded us from identifying patients with AML-MRC due to the presence of an MDS-related cytogenetic abnormality
- There were no ICD-10 codes specific to t-AML or AML-MRC; therefore, these patients were identified based on prior treatment (chemotherapy, radiotherapy) or disease history
- There may be variations in coding quality at the NHS trust level
  - Particularly, AML-MRC with MLD may have been undercoded/underdiagnosed, with only 34 (2%) patients identified out of a total of 1490 patients with AML-MRC in this study. For comparison, in the randomised, phase 3 AZA-AML-001 study that compared treatment with azacitidine versus conventional care regimens in older patients with newly diagnosed AML with >30% bone marrow blasts, 75 out of 262 (29%) AML-MRC patients had MLD alone[8]

Conclusions

- This large, retrospective analysis using the HES database has confirmed the poor historical outcomes for patients diagnosed with t-AML and AML-MRC in England between 2011 and 2016
- Compared with patients with *de novo* AML, those with t-AML or AML-MRC were less likely to receive IC ± HCT and more likely to receive azacitidine or LDAC across most age groups, but most notably for patients aged 60 to 69 years and 70 to 79 years
- OS was significantly shorter for patients with t-AML or AML-MRC compared with patients with *de novo* AML
- More effective agents are needed to address this unmet need

References: 1. Arber DA, et al. *Blood*. 2016;127(20):2391–2405. **2.** Østgård LS, et al. *J Clin Oncol*. 2015;33(31):3641–3649. **3.** Kayser S, et al. *Blood*. 2011;117(7):2137–2145. **4.** European Medicines Agency. Vidaza (azacitidine) [summary of product characteristics]. https://www.ema.europa.eu/en/documents/product-information/vidaza-epar-product-information_en.pdf. Accessed 20 May 2020. **5.** NICE technology appraisal guidance [TA218]. **6.** NICE technology appraisal guidance [TA399]. **7.** Dennis M, et al. *Blood*. 2017;130(Suppl 1). Abstract 3874. **8.** Seymour JF, et al. *BMC Cancer*. 2017;17(1):852.

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