Blood Reviews xxx (xxxx) xxx

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Navigating acute myeloid leukemia towards better outcomes: Treatment pathways and challenges for patients ineligible for intensive chemotherapy

Raffaele Palmieri [a,*], Anna Candoni [b], Francesco Di Raimondo [c], Giuseppe Rossi [d], Massimo Breccia [e], Fabrizio Pane [f], Paola Volpicelli [g], Benedetta Neri [g], Paola Finsinger [g], Morena Caira [g], Felicetto Ferrara [h]

[a] Hematology, Department of Biomedicine and Prevention, University Tor Vergata, Viale Oxford 81, Rome, Italy
[b] Section of Hematology, Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Via Università 4, Modena, Italy
[c] Hematology and BMT Unit, Azienda Ospedaliero Universitaria Policlinico "G. Rodolico-San Marco", Via S. Sofia 78, Catania, Italy
[d] Fondazione Poliambulanza, Via Leonida Bissolati 57, Brescia, Italy
[e] Department of Translational and Precision Medicine, Sapienza University, Via Benevento 6, Rome, Italy
[f] Department of Clinical Medicine and Surgery, University Federico II, Via Pansini 5, Naples, Italy
[g] AbbVie srl, Viale dell'Arte 25, Rome, Italy
[h] Division of Hematology, Cardarelli Hospital, Via Cardarelli 9, Naples, Italy

ARTICLE INFO

Keywords:
Acute myeloid leukemia
Elderly
Epidemiology
Intensive chemotherapy
Unfit
Fitness
Non-intensive chemotherapy

ABSTRACT

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy that affects primarily older individuals. Patients ineligible to receive intensive standard chemotherapy followed by consolidation with/without hematopoietic stem cell transplant have a suboptimal prognosis. In recent years, significant advances have been made in the AML field leading to the development of new anti-leukemic approaches, including lower-intensity therapies specifically developed for patients who are ineligible for intensive chemotherapy. As the available options for this hard-to-manage and historically undertreated patient category are increasing, selecting the best treatment for each patient is crucial and ever more challenging. Accordingly, accurate patient evaluation is required to guide this decision-making process. There is currently no consensus on how to evaluate patients' fitness status, and the available tools that were originally developed for this purpose might not be adequate in the setting of the new treatment options. In this review we describe current management of AML patients unfit for intensive chemotherapy, aiming to highlight current challenges and suggest possible strategies for an accurate therapeutic selection. For this purpose, we will first provide an overview of epidemiology and classification of AML, and then move to current anti-leukemic treatments for unfit patients and the tools used for evaluating patient eligibility for a specific treatment. Finally, we will suggest possible measures to improve the management of AML patients in the era of novel lower-intensity regimens.

1. Introduction

Acute myeloid leukemia (AML) is a disorder of the bone marrow characterized by differentiation arrest and malignant clonal expansion of immature myeloblasts [1–3]. AML has a rapid and fatal course, and it accounts for 62 % of deaths due to leukemia [3]. AML has a relatively low incidence (approximately 3.5 cases per 100,000, in Italy in 2020) [4], which increases with age [5].

In intensive chemotherapy (IC) eligible patients, the standard of care consists of induction (based on the so-called "7 + 3" regimen) in order to achieve complete remission (CR), followed by consolidation therapy with additional chemotherapy or hematopoietic stem cell transplant (HSCT) [6]. Recently, an oral formulation of azacitidine has been approved as maintenance therapy for patients in first complete remission following induction chemotherapy who are not candidates for HSCT or unwilling to receive it [7].

In low or intermediate ELN cytogenetic-molecular risk and CD33-positive blasts, gemtuzumab ozogamicin can be added to the 7 + 3

* Corresponding author.
E-mail addresses: raffaele.palmieri@uniroma2.it (R. Palmieri), anna.candoni@unimore.it (A. Candoni), diraimon@unict.it (F. Di Raimondo), giuseppe.rossi@asst-spedalicivili.it (G. Rossi), breccia@bce.uniroma1.it (M. Breccia), fabrizio.pane@unina.it (F. Pane), paola.volpicelli@abbvie.com (P. Volpicelli), benedetta.neri@abbvie.com (B. Neri), paola.finsinger@abbvie.com (P. Finsinger), morena.caira@abbvie.com (M. Caira).

https://doi.org/10.1016/j.blre.2025.101288

Available online 9 April 2025

regimen [8,9], whereas for patients with *FLT3*-mutated AML the addition of midostaurin to "3 + 7" regimen is indicated. An alternative intensive induction strategy is a liposomal formulation of anthracycline and cytarabine (CPX-351), approved in Europe in 2018 for the treatment of adults with newly diagnosed, therapy-related AML, or AML with myelodysplasia-related changes [10]. Despite these advancements, there's still an urgent need to improve the unsatisfactory outcomes of *TP53* mutated AMLs, regardless of the treatment delivered.

As the efficacy and tolerability of induction therapy decrease with age, [8] older patients need to be carefully evaluated for their fitness to receive intensive anti-leukemic therapy. [11] This is a critical step since evidence from studies describing AML treatment patterns in clinical practice has shown that a great proportion of older patients are undertreated or untreated following diagnosis. [12–20] In fact, a study using US Medicare data (2007–2017) found that of the 4154 patients with AML aged ≥66 years, 43.2 % received chemotherapy, 33.8 % best supportive care, and 23.1 % no therapy at all, within 60 days of diagnosis. [15] In another recent international retrospective chart review, including 1762 patients with AML considered ineligible to receive intensive chemotherapy, more than one-quarter (n = 452) received supportive care only. [19] Finally, a literature review specifically addressing real-world patterns of AML undertreatment demonstrated that the proportion of patients not receiving any active antileukemic therapy ranged from 10 % to 61 % in the US and from 24 % to 35 % in Europe. [13] Over the past two decades, our knowledge of AML molecular biology has considerably increased, resulting in the update of disease classification systems and development of new therapies. [6] Starting in 2017, several drugs have been either granted approval for the treatment of patients with AML or are under evaluation in clinical trials [6,21] Consequently, assessing the fitness of patients for intensive, non-intensive, or targeted therapy is an issue of ongoing interest. [11] Several tools for establishing patient fitness for intensive chemotherapy are available, although no consensus exists on which one should be better adopted in daily clinical practice. [11]

The aim of this paper is to review the current state of AML management of patients not eligible for intensive chemotherapy, starting from the available Italian literature and then widening to an international level. To this purpose we will first provide an overview of current epidemiology and classification of AML. We will then discuss the emerging anti-leukemic treatment options and the challenges of assessing patient fitness for these lower-intensity regimens. Measures for improving the management of AML patients unfit for intensive chemotherapy will also be addressed.

2. Methods

PubMed was searched using combinations of the following terms: "acute myeloid leukemia" AND "epidemiology", "incidence", "prevalence", "survival", "mortality", "fitness". Retrieved articles (up to January 2024) were first selected based on their titles. Articles identified as potentially interesting were further screened by evaluating their abstract; their full text was obtained if the abstract content was found to be relevant.

3. Epidemiology of acute myeloid leukemia

Table 1 summarizes the current epidemiology data of AML worldwide over the past five decades, with a predominance of the period 2000–2015. The studies are heterogeneous in terms of data source, quality, and reported data. Less than half of the reports are based on national cancer registries, with other sources including insurance claims databases, registries of other diseases, and patient medical charts. Only a few countries have comprehensive and regularly updated registries or initiatives specifically dedicated to AML. [3,5,12,22,23]) In Italy, data mostly come from the Italian Association of Cancer Registries (AIRTUM). [24]

Despite da heterogeneity, several general trends can be observed. The annual incidence of AML has increased globally, is higher in men than in women, and rises significantly with age, peaking around 80 years. [3,5,25,26,29–33] Two reports, one from the US and one from Italy, indicated higher incidences rates than the average reported in literature, possibly due to demograpich factors and data collection methods. [24,29–35] The incidence of AML is generally higher in Western countries [36] and is expected to increase worldwide in the future due to the progressive aging of the population and the prolonged survival of patients with solid tumors treated with therapies that significantly increase the risk of secondary AML development. [37,60]

Survival and mortality data show that AML remains a fatal disease, particularly among patients over 60–70 years and those ineligible for intensive chemotherapy and HSCT. [15,17,24]. Hjort Jakobsen et al. analyzed survival trends in Denmark in 2000–2016 and highlighted significant improvements in 2-year, age-adjusted overall survival, which increased from 22 % in 2002 to 26 % in 2006 and up to 31 % in 2016. [12] In several studies, increases in survival appeared to be more consistent among women and to decrease with advancing age. [25,38–40] Regarding the impact of age on short- and long-term outcome, survival improvements were reported especially in the age group 50–75 years, while the age group ≥75 years had virtually no significant changes over time. [19,41–43]

4. 2022-updates of acute myeloid leukemia classification

The continuous progress in the molecular analysis of hematologic malignancies and the advances in our understanding of leukemia biology require a regular update of existing disease classifications. In 2022, a new version of the World Health Organization (WHO) classification of myeloid and histiocytic/dendritic neoplasms was published. [61,62] At the same time, a new classification of myeloid neoplasms and acute leukemias – the International Consensus Classification (ICC) – was released. [63] Table 2 summarizes the WHO 5th edition and the ICC-2022 classifications of AML.

The main changes introduced by the 5th edition of the WHO classification, are

- 20 %-blast cut-off decreased to <10 % for most diagnoses with defining genetic abnormalities;
- incorporation of new/rare AML subtypes under "AML with other defined genetic alterations".

The 2022-ICC classification, while retaining most of the previously WHO-defined AML types, highlights the importance of genetic characteristics, since these features seem to have a major impact on disease phenotype and disease outcomes. Additional features, including therapy-relatedness, antecedent MDS or MDS/MPN, and germline predisposition (inherited predisposition to AML), are included in the ICC-2022 classification as "qualifiers of the primary diagnosis". [6,65] Therefore, the prior AML types "therapy-related myeloid neoplasms" and "AML with myelodysplasia-related changes" are no longer present as stand-alone entities, highlighting the evidence that genetic characteristics are more relevant than clinical history in classifying biologically distinct AML types. Furthermore, to underline the potential evolution from MDS to AML, the ICC-2022 classification includes the new MDS/AML category that defines cases with 10 % to 19 % blasts (previously called MDS with excess blasts [EB]-2). [65]

Of note, the European Leukemia Net (ELN) recommendations for the diagnosis and management of AML, updated in 2022, are based on the ICC 2022 classification and provide an improvement on previous genetic risk stratification, revised response criteria and treatment recommendations. [6] However, while this genetic stratification is known to be accurate for young patients, it does not appear to be appropriate for patients over 60 years. For this reason, the ELN has recently proposed a revised genetic risk stratification, focusing on patients receiving less

Table 1
Epidemiology of acute myeloid leukemia.

Ref n.	Study	Country	Period	Population	Incidence/prevalence	Survival/mortality
[3]	Shallis et al., 2019	US	1975–2016	▪ SEER database	▪ Overall incidence: 3.66 per 10^5; 4.55 per 10^5 in males and 3.04 per 10^5 in females ▪ From 2010, overall incidence consistently >4.2 per 105 ▪ Age-adjusted incidence for pts. aged ≥65 yrs.: 20.1 per 105 person yrs.; 2.0 per 105 person yrs. for those aged <65 yrs. ▪ Prevalence in 2016: 19 per 105 population	▪ Mortality rate relatively stable over 2005–2016 ▪ Based on 2011–2016 data, mortality rate: 2.8 per 105 person yrs. ▪ Median overall survival in 2016: 8.5 months; 2-yr and 5-yr survival 32 % and 24 %, respectively
[5]	Juliusson et al., 2009	Sweden	1997–2005	▪ Swedish Adult Acute Leukemia Registry ▪ $N = 2767$	▪ Incidence increases with age ▪ Marked increasing trend from ages 60–64 yrs. ▪ Peak incidence at 80–84 yrs	▪ Deaths within 30 days from diagnosis (early deaths): 19 % ▪ Early deaths in pts. treated with ICT 10 %; 34 % in pts. treated with palliative therapy ▪ No improvement in crude OS
[12]	Hjort Jakobsen et al., 2021	Denmark	2000–2016	▪ Danish National Acute Leukemia Registry ▪ $N = 3820$	na	▪ Significant improvements in age-adjusted OS; 2-yr age-adjusted OS in 2002, 22 %; in 2010, 26 %; in 2016, 31 % ▪ OS improvements only in pts. aged ≥50; no differences between males and females
[15]	Li et al., 2022	US	2007–2017	▪ Medicare hematologic cancer data ▪ Elderly patients (≥ 66 yrs) newly diagnosed with AML with ≥1 ineligibility criteria for ICT ($N = 4152$) ▪ 43.2 % treated with CT (intensive 58.8 % and non-intensive 41.2 %), 33.8 % received best supportive therapy, 23.1 % received no therapy	na	▪ Median OS: 1.9 months for patients treated with ICT; 3.8 months with non-intensive chemotherapy; 1.0 months for best supportive care
[17]	Martinez-Cuadrón et al., 2021	Spain	1999–2013	▪ Spanish PETHEMA AML registry ▪ Pts aged ≥60 yrs. ($N = 3637$)	na	▪ Median OS, 4.7 months; 1-yr OS, 29 %; 5-yr OS, 7 % ▪ Median OS, 8.6 months for pts. treated with ICT; 7.8 months with non-intensive therapy; 1.2 months with supportive care only ▪ Crude 5-yr disease-specific survival: 18 %
[22]	Beckmann et al., 2022	Australia	1980–2016	▪ South Australian Cancer Registry ▪ 2814 pts. diagnosed with AML	na	▪ Steadily improvement of 5-yr survival from 9 % for pts. diagnosed during 1980–1984 to 23 % for those diagnosed during 2010–2016 ▪ Improvement more substantial in pts. aged <50 yrs
[25]	Fuji et al., 2021	Japan	1975–2017	▪ Osaka Cancer Registry ▪ 9706 cases of AML	▪ Steady increase in annual number of cases (150 cases/yr around 1980 and 300 cases/yr around 2010) ▪ Increasing trend also in age-adjusted incidence rate ▪ Overall, age-adjusted incidence rate < 2.5 per 105 person yrs	▪ 3-yr OS in pts. with APL: 14.9 % in 1975–1989, 39.6 % in 1990–2001, 61.2 % in 2002–2010, 68.1 % in 2011–2017 ▪ 3-yr OS in pts. with non-APL AML: 8.9 % in 1975–1989, 18.3 % in 1990–2001, 27.6 % in 2002–2010, 27.3 % in 2011–2017 ▪ Improvements in OS rates more marked in pts. aged ≤60 yrs

(*continued on next page*)

Table 1 (*continued*)

Ref n.	Study	Country	Period	Population	Incidence/prevalence	Survival/mortality
					▪ Crude annual incidence: 3.3 per 10^5	▪ Median OS: 5.6 months; in pts. treated aggressively, median OS: 12.2 months ($p < 0.0001$)
[26]	Gangatharan et al., 2013	Australia	1991–2005	▪ Western Australia Cancer Registry ▪ 987 pts. with AML	▪ Significant increase from 2.8 in 1991 to 4.2 in 2005 ($p < 0.001$)	▪ Median OS in pts. aged >60 yrs.: 1.7 months and 6.8 months in those treated aggressively ($p < 0.0001$)
					▪ Age-standardized incidence was similar, with a similar increasing trend	▪ In pts. treated aggressively, 5- and 10-yr OS rates of 9 % and 5 %, respectively
[27]	Granfeldt Østgård et al., 2015	Denmark	2000–2013	▪ Danish National Acute Leukemia Registry ▪ 3055 pts. diagnosed with AML ▪ 73.6 % had de novo AML; 19.8 % sAML ▪ 51.3 % treated with ICT	na	▪ Among pts. treated with ICT, inferior survival in pts. with sAML or prior cytotoxic exposure versus pts. with de novo AML
[28]	McGregor et al., 2016	UK	2007–2011	▪ Population-based retrospective study to assess the impact of age and genetics on outcome ($N = 416$ diagnosed with AML; 363 analyzed)	▪ Annual population incidence: 2.68 per 10^5	▪ 4-yr OS, 82 %, 36 %, and 18 % for favorable, intermediate, and adverse cytogenetic groups, respectively ▪ Median survival of pts. aged >60, intensively treated: 12 months; 2-yr survival: 31 % ▪ 5-yr OS 60 % in intensively treated pts. aged >60 with intermediate risk cytogenetics and FLT3–/NPM1+ status
[23]	Roman et al., 2016	UK	2004–2015 (diagnosed in 2004–2013)	▪ Population-based cohort with myeloid malignancies, established in 2004 ▪ $N = 5231$; 1411 pts. with AML	▪ Crude incidence rate per 10^5: 4.39; 4.94 in males and 3.87 in females	▪ 5-yr OS and RS, 12.9 % and 14.7 %, respectively (worse survival than for any other myeloid malignancy considered)
[24]	Calabria et al., 2023	Italy	2017	▪ Data from the Italian Ricerca e Salute administrative database ▪ 368 pts. newly diagnosed with AML in 2017	▪ Incidence in 2017: 9 per 10^5 ▪ Prevalence: 12.5 per 10^5	▪ 1-yr and 2-yr OS in pts. treated with ICT: 41.1 % and 26.9 %, respectively; median survival, 7.8 months ▪ In pts. unfit for ICT: 25.6 % and 18.7 %, respectively; median survival, 1.2 months
[29]	Bassig et al., 2022	Hong Kong	2014–2016	▪ Pts with myeloid malignancies diagnosed at four hospitals ▪ 705 cases of AML	▪ Overall incidence rate: 2.23 per 10^5; 2.60 for men and 1.92 for women (w/m ratio, 0.7)	na
[30]	Broccia et al., 2004	Italy	1974–1993	▪ Resident population of Sardinia ▪ Newly diagnosed cases of hematologic malignancies ($N =$ 7264, 703 cases of AML)	▪ World-standardized incidence rates per 10^5 person yrs.: 2.07 and 2.42 in males, and 1.17 and 1.73 in females, in the 1974–1983 and 1984–1993 decades, respectively ▪ Incidence rates in pts. aged >75 yrs.: 10.16 and 18.09 in males, and 3.23 and 5.75 in females, in the first and second decade, respectively	na
[31]	Busco et al., 2016	Italy	2000–2010	▪ Data from the Italian Association of Cancer Registries (AIRTUM)	▪ Annual crude incidence rate per 10^5: 4.79 (5.22 and 4.38 for males and females, respectively) ▪ Annual crude incidence rate per 105: age 0–54, 1.49; age 55–64, 5.60; age $\geq$ 65, 15.58	▪ 1-yr survival: 39 % ▪ 5-yr survival: 18 %
[32]	Shysh et al., 2017	Canada	2011–2015	▪ Retrospective cohort of pts. with AML, Calgary Metropolitan Area	▪ Incidence rate: 2.79 cases per 10^5 person yrs. ▪ Higher incidence in males versus females; ratio male/female, 1.25	na
[33]	Solans et al., 2022	Spain	2002–2013	▪ Spanish network of cancer registries	▪ AS incidence rate: 3.91 per 10^5 person yrs.; 4.75 in men and 3.28 in women (ratio 1.45)	na

(*continued on next page*)

Table 1 (*continued*)

Ref n.	Study	Country	Period	Population	Incidence/prevalence	Survival/mortality
[34]	Pulsoni et al., 2004	Italy	1992–1998	■ Myeloid neoplasm cases (N = 17,522; 4498 with AML) ■ GIMEMA database ■ 1005 pts. aged >60 yrs. ■ 621 treated with ICT; 384 with non-intensive therapies or supportive care		■ Median survival: 7 months in pts. treated with ICT and 5 months in pts. treated with non-intensive therapies/ supportive care ($p < 0.0001$) ■ In the >70-yr age group, no significant difference in survival with ICT vs non-intensive therapies/ supportive care
[35]	Turberville et al., 2014	US	2012	■ Retrospective analysis of insurance claims ■ 15,976 pts. with AML, 75 % aged ≥65 yrs	■ 1-yr incidence: 9.074 per 10^5 person ■ 1-yr prevalence rate: 0.05 % ■ ASIR 1990: 1.35 per 10^5 ■ ASIR 2017: 1.54 per 10^5	na
[36]	Dong et al., 2020	Global	1990–2017	■ Global Burden of Disease online database ■ Leukemia data, including AML data	■ AML accounted for 18 % of all leukemia cases in 1990 and for 23.1 % in 2017 ■ High incidence reported mostly in Europe	na
[37]	Ocias et al., 2016	Denmark	1980–2012	■ Danish NORDCAN database	■ Incidence rate: 15–20 per 10^5 person yrs. among pts. aged ≥70; 2–3 per 10^5 person yrs. among pts. aged <70	■ Increased 1-yr relative survival in pts. aged <70 over the observation period by 40 %; by 10 % in pts. aged ≥70 ■ 5-yr relative survival improvements only for pts. aged <70
[38]	Chien et al., 2023	Taiwan	2001–2015	■ Retrospective cohort study on three Taiwan databases ■ 9949 pts. with newly diagnosed AML	■ Overall age-adjusted incidence: 2.44 per 10^5 person yrs	■ Median OS: 18 months for pts. aged <65 yrs. and 5 months for pts. aged ≥65 yrs ■ Net survival: 1-yr, 41 %; 3-yt, 24 %; 5-yr, 20 % ■ 5-yr survival males/ females: age 15–44, 57 %/61 %; age 45–54, 46 %/45 %; age 55–64, 27 %/32 %; 65–74, 9 %/11 %; 75–99, 3 %/4 %
[39]	Coviello et al., 2017	Italy	2005–2009	■ Data from the Italian Association of Cancer Registries (AIRTUM)	na	
[40]	Philip et al., 2015	India	2012–2014	■ All pts. with a diagnosis of AML presenting at the study center ■ N = 380, 12.3 % aged ≤15 yrs., 71.3 % aged between 15 and < 60 yrs., and 16.3 % aged ≥60 yrs	na	■ 1-yr OS: 70.4 %, 55.6 %, and 42.4 % for pts. aged ≤15, 15–59, and ≥ 60 yrs., respectively
[41]	Juliusson et al., 2019	Sweden	1997–2016	■ Swedish AML registry ■ N = 6994	na	■ Improved survival in the age group 50–75 yrs. ■ No improvement in younger or older pts. ■ Improvement greater in men than in women
[42]	Sant et al., 2014	Europe	1992–2007 (diagnosis); follow-up up to December 2008	■ EUROCARE data ■ 135,414 cases of myeloid hematologic malignancies diagnosed 1996–2007; 48,086 AML cases	na	■ Modest increase in AS 5-yr RS from 1997 to 99 (12.6 %) to 2006–08 (14.8 %; $p < 0.0001$) ■ Greatest survival improvement in age group 65–74 yrs. ■ Virtually no improvement in age group ≥75 yrs ■ AS mortality rate per 10^5 pt. yrs.: 2.0 in 2001–2007 and 1.9 in 2008–2013
[43]	Schnegg-Kaufmann et al., 2018	Switzerland	2001–2013	■ Swiss Cantonal Cancer Registries ■ 2351 new AML cases	■ AS incidence rate: 3.0 per 10^5 person yrs. ■ AS incidence rate stable over 2001–2007 and 2008–2013	■ Modest improvement of 5-yr survival from 2001 to 2007 (19.2 %) to 2008–2013 (23.3 %) ■ Marked 5-yr survival improvement in age group 65–74 yrs.: from 5.2 % in 2001–2007 to 13.5 %, $p < 0.001$ in 2008–2013
[44]	Maynadié et al., 2011	France	1980–2004	■ Registry of Hematologic Malignancies of the Côte d'Or	■ Annual incidence rate per 10^5: 2.5	■ Median OS: 8.9 months ■ Observed 20-yr survival rate: 12 %

(*continued on next page*)

Table 1 (*continued*)

Ref n.	Study	Country	Period	Population	Incidence/prevalence	Survival/mortality
				Department ■ 468 pts. with AML		■ Median OS: 6 months
[45]	Lerch et al., 2009	Switzerland	1984–2003	■ Pts newly diagnosed with AML in Southern Switzerland (N = 128) ■ 35 pts. treated with beet supportive care and/or palliative CT; 93 pts. treated with ICT	■ Annual incidence: 2.6 per 10^5	■ 2-yr OS: 16 % ■ Median OS in pts. treated with supportive care/palliative CT: 2 months ■ 2-yr OS for pts. treated with ICT: 40 % for those aged <60 yrs. and 12 % for those aged ≥60 yrs
[46]	Juliusson et al., 2017	Sweden	1997–2013	■ Swedish cancer registries ■ AML pts. diagnosed in 1997–2013 and surviving on January 1, 2014 (N = 1337, 20.3 %)	■ Overall prevalence: 13.7 per 10^5	na
[47]	Sant et al., 2010	Europe	2000–2002	■ 44 European cancer registries of hematologic malignancies ■ 21.796 myeloid malignancy cases; 8107 cases of AML	■ Crude incidence rate of AML: 3.62 per 10^5 person; 3.90 in males, 3.35 in females ■ Increasing with age	na
[48]	Visser et al., 2012	Europe	1995–2002	■ RARECARE data ■ 29,719 observed cases of AML	■ Annual crude incidence rate: 3.7 per 10^5 (4.0 in males and 3.4 in females) ■ Incidence rates per 105 in ages groups: 0–14 yrs., 0.7; 15–24 yrs., 0.8; 25–64 yrs., 2.4; ≥65 yrs., 13.7	■ 1-yr RS: 37 %; 5-yr RS: 19 %
[49]	Song et al., 2018	US	2001–2013	■ SEER database ■ 32,941 pts. with AML	na	■ Different survival for AML subtypes ■ Demographic factors (race/ethnicity, socioeconomic status, marital status) can influence survival
[50]	Ghazawi et al., 2019	Canada	1992–2010	■ Population-based cancer registries ■ 18,085 cases of AML	■ Average annual incidence rate: 3.061 per 10^5 ■ In industrial areas, > 3 times higher incidence than the national average	■ Average annual mortality rate: 2.053 per 10^5
[51]	Capra et al., 2007	Brazil	1996–2000	■ Pts record of referral hospitals ■ 532 pts. with de novo AML	■ Annual incidence: 1.11 cases per 10^5; 0.5–1 per 10^5 up to the age of 45 yrs. and 3.5 cases per 10^5 for ages ≥70 yrs	■ Mean 5-yr survival: 17 %
[52]	Bekadja et al., 2011	Algeria	2006–2010	Nationwide survey across 15 hematology centers 1426 AML cases ■ Public and private pt. data archives	■ Annual incidence: 0.91 per 10^5 ■ Continuous increase of incidence from 2006 to 2010	na
[53]	Oelofse et al., 2018	South Africa	2004–2013	■ 3603 cases of hematologic malignancies	■ Annual AS incidence rate: 0.57 per 10^5	na
[54]	Matsunaga et al., 2012	Japan	2003–2008	■ 371 cases of AML and related precursor neoplasms ■ Retrospective population-based cohort study, Miyazaki Prefecture ■ 221 pts. with AML (10 children); 203 adults included in the analysis (10 APL pts. and 193 non-APL pts)	■ Annual incidence: 3.2 per 10^5	■ 5-yr OS APL pts.: 88.9 % ■ 5-yr OS non-APL pts.: 21.1 %
[55]	Huang,et al., 2022	Taiwan	2006–2015	■ Taiwan Cancer Registry Database ■ 7403 pts. diagnosed with AML	■ Increase of crude annual incidence from 2.78 (2006) to 3.21 (2015) per 10^5 ■ Decrease of ASR from 2.47 (2006) to 2.41 (2015) per 10^5 ■ Peak of incidence in the age group >60 yrs	na

(*continued on next page*)

Table 1 (*continued*)

Ref n.	Study	Country	Period	Population	Incidence/prevalence	Survival/mortality
[56]	Wanitpongpun et al., 2021	Thailand	2014–2017	▪ 679 pts. with AML from nine academic hospitals; 61 pts. (9 %) with APL, 618 pts. (91 %) with non-APL AML	na	▪ Median OS: 6.5 months ▪ 3-yr OS in APL pts.: 88.2 %; in non-APL pts.: 24.5 % ($p < 0.01$)
[57]	Alshemmari et al., 2022	Kuwait	2014–2020	▪ Kuwait Cancer Center ▪ 281 cases of AML (8.9 % with APL)	▪ Incidence rate: 0.55–1.1 per 10^5 (0.49–1.6 for females, 0.5–1.1 for males) ▪ Increasing trend of AML incidence over 2014–2020	▪ Median OS: 37 months
[58]	Aitbekov et al., 2022	Kazakhstan	2017–2020	▪ Pts diagnosed with AML in five regions of the country ▪ $N = 334$	▪ WHO-standardized annual incidence rate across the five regions: 1.39–2.43 per 10^5	na
[59]	Khondkaryan et al., 2022	Armenia	2012–2018	▪ National Institute of Health of the Republic of Armenia ▪ 478 new cases of AML	▪ Age-standardized annual incidence rate: 1.9 per 10^5 (male/female ratio, 1.1) ▪ No significant changes in incidence trends over 2012–2018	na

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AS, age-standardized; ASIR, age-standardized incidence rate; CT, chemotherapy; ICT, intensive chemotherapy; MDS, myelodysplastic syndrome; na, not available; OS, overall survival; pt., patient; RS, relative survival; sAML, secondary AML; vs, versus; yr, year.

intensive therapies (hypomethylating agent (HMA)-based regimens alone or in combination with either the *BCL2* inhibitor venetoclax (VEN), or azacitidine (AZA) with the IDH1 inhibitor ivosidenib (IVO) for IDH1-mutated AML). [66]

5. Current management of patients unfit for intensive chemotherapy

5.1. Fitness assessment, state of the art, and current challenges

Considering the increase in therapeutic alternatives, balancing potential treatment-related toxicities and expected benefits has progressively become of central importance. This process aims to identify which treatment, among the many available, would better "fit" a specific clinical context. [63] Nevertheless, acknowledging the importance of this evaluation process has not translated yet into widely adopted guidelines. Furthermore, there is still no consensus on how fitness should be measured and translated into practical clinical indications. [66].

Recently an international panel of experts on behalf of the ELN, has published recommendations on fitness in patients with AML, to provide tools for a general definition of fitness/unfitness and to identify and categorize individual factors that contribute to its definition. [67]

For several decades, intensive chemotherapy was the only valuable option and being "fit" was considered the green light for initiating a curative-intended program. [63] Conversely, being qualified as "unfit" automatically translated into palliative care delivery. [68]

Nowadays, different fitness levels correspond to different treatment intensities. Accordingly, patients should be considered "fit for" a specific treatment strategy. The diverse intensities of available treatments emphasize the necessity of recognizing additional fitness levels extending beyond the conventional categories of "fit," "unfit," and "frail." Therefore, patients should be considered "eligible" for a specific treatment strategy based on clinical fitness and biological factors, with a clear explanation of the treatment approach and the provision of alternative options [67] and in favor of a more appropriate "how to best treat" approach.

The unsatisfactory long-term outcomes in older patients are related to distinct disease- (e.g. biological) and patient-related (e.g. clinical) features. [69] On one hand, AML in older patients is characterized by a greater extent of unfavorable cytogenetic features such as unbalanced chromosome translocations, aberrant karyotypes, and molecular abnormalities. [8,70] On the other, higher comorbidity burden, lower performance status (PS), or even advanced age by itself, justify the reduced tolerability to active treatment observed in older individuals. [8]

Although chronological age may be considered as a surrogate for functional reserve, it is worth noting that establishing an absolute cut-off to identify elderliness/unfitness may be arbitrary, as older age is often reached in a good general condition. [71] Indeed, advanced age has been associated with worse outcome particularly in patients with additional risk factors, such as poor PS. [5,72] To a greater extent, lower PS translates into reduced tolerability to active treatment irrespective of age. [8] Nevertheless, PS assessment suffers from critical intrinsic limitations, including its subjective nature. [71] As proof of this concept, a proportion of patients with poor PS (though small) achieve and maintain a disease-free status without experiencing relevant toxicities. [5] Hence, as already observed with age, PS as a single parameter is insufficient to evaluate fitness status.

Past medical history also needs to be considered when measuring fitness. Concurrent medical conditions may be exacerbated by anti-leukemic therapies, possibly resulting in severe side effects or even early mortality. [73] This may be particularly relevant in older individuals, as they are frequently affected by several comorbidities. [65] Multiple scores have been designed to measure comorbidity burden, including the Charlson Comorbidity Index (CCI). [74] This tool aims not only to enlist each patient's comorbidities but also to quantify their severity. Nevertheless, it is not uncommon that a single severe comorbidity (accounting for a modest CCI) may lead to mortality early after treatment. [68,73] In contrast, patients with multiple mild comorbidities (and so with higher CCI) can still be able to achieve complete response without significant complications. Therefore, objectifying comorbidity status may not necessarily be informative of fitness level.

Given the uncertain impact of single factors on patients' fitness status, several multiparametric tools (also called "fitness scores") are commonly adopted in daily clinical practice. Comprehensive geriatric assessment (CGA) examines health-related factors (such as comorbidities, physical and cognitive function) specifically in older individuals. [75] Several studies in patients with hematologic malignancies have shown that CGA can intercept frailness also in patients who are apparently eligible for intensive chemotherapy. [76] However, since CGA was not originally designed for evaluating fitness level, its applicability is limited as it does not provide clear information on how to modulate treatment intensity according to fitness status. Besides CGA, more "pure" fitness scores are commonly utilized. [77–79] Among these, the so-called Ferrara criteria (SIE SIES GITMO consensus criteria) combine

Table 2
Classifications of acute myeloid leukemia.

WHO CLASSIFICATION 5th edition [64]	
Acute myeloid leukemia with defining genetic abnormalities	
AML with *PML::RARA* fusion	
AML with *RUNX1::RUNX1T1* fusion	
AML with *CBFB::MYH11* fusion	
AML with *DEK::NUP214* fusion	
AML with *RBM15::MRTFA* fusion	
AML with *BCR::ABL1* fusion	
AML with *KMT2A* rearrangement	
AML with *MECOM* rearrangement	
AML with *NUP98* rearrangement	
AML with *NPM1* mutation	
AML with *CEBPA* mutation	
AML, myelodysplasia-related[a]	
Defining cytogenetic abnormalities:	
• Complex karyotype (≥3 abnormalities)	
• 5q deletion or loss of 5q due to unbalanced translocation	
• Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation	
• 11q deletion	
• 12p deletion or loss of 12p due to unbalanced translocation	
• Monosomy 13 or 13q deletion	
• 17p deletion or loss of 17p due to unbalanced translocation Isochromosome 17q	
• idic(X)(q13)	
Defining somatic mutations: *ASXL1*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*	
AML with other defined genetic alterations	
Acute myeloid leukemia, defined by differentiation	
AML with minimal differentiation	
AML with maturation	
Acute basophilic leukemia	
Acute myelomonocytic leukemia	
Acute monocytic leukemia	
Acute erythroid leukemia	
Acute megakaryoblastic leukemia	
Myeloid sarcoma[b]	
ICC CLASSIFICATION (49)	
Acute myeloid leukemia	**Blast percentage required at diagnosis**
APL with t(15;17)(q24.1;q21.2)/*PML::RARA*	≥ 10 %
APL with other *RARA* rearrangements	≥ 10 %
AML with t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*	≥ 10 %
AML with inv. [16](p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*	≥ 10 %
AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*	≥ 10 %
AML with other *KMT2A* rearrangements	≥ 10 %
AML with t(6;9)(p22.3;q34.1)/*DEK::NUP214*	≥ 10 %
AML with inv. [3](q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2; MECOM(EVI1)*	≥ 10 %
AML with other *MECOM* rearrangements	≥ 10 %
AML with other rare recurring translocations	≥ 10 %
AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1*	≥ 20 %
AML with mutated *NPM1*	≥ 10 %
AML with in-frame bZIP *CEBPA* mutations	≥ 10 %
AML and AML/MDS with mutated *TP53*	10–19 % (MDS/AML) and ≥ 20 % (AML)
AML and AML/MDS with myelodysplasia-related gene mutations Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*	10–19 % (MDS/AML) and ≥ 20 % (AML)
AML with myelodysplasia-related cytogenetic abnormalities Defined by detecting a complex karyotype, del(5q)/t(5q)/ add(5q), 27/del(7q), 18, del(12p)/t(12p)/add(12p), i(17q), 217/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities	10–19 % (MDS/AML) and ≥ 20 % (AML)
AML not otherwise specified	10–19 % (MDS/AML) and ≥ 20 % (AML)
Myeloid sarcoma[b]	–
Diagnostic qualifiers	
Therapy-related	
Prior chemotherapy, radiotherapy, immune interventions	
Progression from MDS	
MDS should be confirmed by standard diagnostics	
Progression from MDS/MPN	
MDS/MPN should be confirmed by standard diagnostics	
Germline predisposition	

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

[a] The presence of one or more cytogenetic or molecular abnormalities listed and/or history of MDS or MDS/MPN are required for diagnosing AML myelodysplasia-related.

[b] A tissue-based manifestation of AML.

clinical parameters such as age, comorbidities, and PS to categorize AML patients into fit, unfit, and frail to treatments of different intensity. [77] These criteria were retrospectively applied to two large cohorts of patients with AML, aiming to evaluate their applicability in daily clinical practice. [80,81] In both studies, a good concordance between fitness level and treatment actually received (e.g. intensive chemotherapy for IC eligible patients, non-intensive therapies for IC inelegible patients, and supportive therapy for frail ones) was observed. The three groups were clearly distinct in terms of survival, hinting that these criteria could represent a valid tool to tailor the intensity of available treatments. [80,82] Furthermore, when retrospectively applied to a large cohort of intensively treated AML patients, the Ferrara criteria accurately predicted mortality at early timepoints from induction (28 and 100 days). [82] SIE/SIES/GITMO criteria have been utilized also in several clinical trials investigating novel agents, aiming to identify patients who are less likely to tolerate IC and that could, therefore, be candidate to less intensive schemes.

Alongside the Ferrara criteria, many other tools for fitness assessment are currently available. [78,79] Most of these scores were retrospectively tested on intensively treated patients, showing good to very good performance in predicting putative surrogates of fitness status, such as early mortality and overall survival. [78,79] In other words, the reliability of these scores is almost exclusively limited to identifying patients for whom an intensive approach can lead to an excess of toxicity. How to choose the most appropriate non-intensive approach remains largely unexplored. The “non-intensive” group of therapies currently includes a miscellanea of both combination therapies (low-dose cytarabine/hypomethylating agents plus venetoclax, low-dose cytarabine plus glasdegib, hypomethylating agents plus *IDH1* inhibitors) and monotherapies (hypomethylating agents [intravenous, subcutaneous, oral], low-dose cytarabine). [68] All these treatments share the same clinical indication, as they have all been licensed for patients considered ineligible for intensive chemotherapy. Such heterogeneity may be explained by the lack of robust data on the safety profile of new combination strategies that, despite being less intensive than conventional chemotherapy, are still (intuitively) more intensive than hypomethylating agents or low-dose cytarabine only. Identifying intermediate levels of fitness and possibly designing new fitness scores (or recalibrating existing ones) may be required to optimize the approach to patients ineligible for IC.

5.2. *Available treatments for patients unfit for intensive chemotherapy*

According to the 2022-updated ELN recommendations, treatment options for newly diagnosed patients ineligible for IC include the following regimens: azacitidine or decitabine plus venetoclax, low-dose cytarabine plus venetoclax, azacitidine plus ivosidenib (AML with *IDH1* mutation), ivosidenib monotherapy (AML with *IDH1* mutation), and best supportive care with hydroxyurea and transfusion support for patients who cannot tolerate any anti-leukemic therapy, or do not wish any therapy. [6] According to the 2.2024 version of the National Comprehensive Cancer Network (NCCN) guidelines, the preferred options for lower-intensity regimens, in absence of *IDH1* mutation, include

venetoclax plus hypomethylating agents azacitidine or decitabine (Category 1 recommendation). [2] Other recommended options are low-dose cytarabine plus venetoclax or glasdegib. [2] Patients ineligible for combination or targeted therapy can receive hypomethylating agents in monotherapy, gemtuzumab ozogamicin monotherapy, or low-dose cytarabine. [2] Ivosidenib and enasidenib are preferred options for patients with *IDH1*- and *IDH2*-mutated AML, respectively. [2]

The combination of azacitidine with venetoclax has become the standard of care for patients with AML ineligible for IC. The results of the phase 3 trial VIALE-A in previously untreated AML patients who are ineligible to IC and/or because of (≥ 75 years) and/or fitness status have shown that the addition of venetoclax to azacytidine was associated with a significant improvement in median overall survival compared to azacitidine plus placebo (14.7 months versus 9.6 months, HR for death 0.58; 95 % CI 0.465 to 0.723; $p < 0.001$). [83,84] Estimated 24-month overall survival rates were 37.5 % versus 16.9 % with venetoclax-azacitidine and placebo-azacitidine, respectively. [84] Rates of complete remission were 38.8 % versus 17.9 %, respectively ($p < 0.001$) with high proportion of patients who achieved transfusion independence in experimental arm 59.8 % (95 % CI, 53.9 to 65.5) versus 35.2 % (95 % CI, 27.4 to 43.5) of those in the control group ($P < 0.001$). [84] Moreover, venetoclax plus azacitidine appears to have a positive impact on the health-related quality of life (HRQoL), helping to preserve the functioning and overall health status. [85] Evidence from phase 1b/2 studies suggests that similar results are achieved with the addition of venetoclax to the hypomethylating agent decitabine. [86] For patients who do not tolerate hypomethylating agents, the ELN recommendations suggest the combination of venetoclax with low-dose cytarabine, as an alternative. [6,87] Following FDA approval, venetoclax in combination with either HMAs or low dose cytarabine was extensively investigated in real world settings. Hoff et al. reported a real-world ORR of 55 % and a median overall survival OS of 13 months in 112 patients, slightly inferior than those observed in the VIALE-A trial. [88] A systematic review and meta-analysis by Ucciero et al. demonstrated a median survival of 9.37 months for patients treated with VEN + HMA in real-world settings, improving to 11.5 months when restricted to studies focusing on VEN + AZA combination. These discrepancies may be attributable to different characteristics of enrolled patients or to a non-optimal adherence to therapy and the subjective determination of "fitness" [89]. For example, studies including series of patients that were older and/or with higher comorbidity than those from the VIALE-A trial, as in Abaza's multicenter analysis, revealed a median OS of 9.5 months, notably lower than VIALE-A outcomes. [90] Conversely, the Italian observational GIMEMA AML2320 trial included patients with similar characteristics to those from the VIALE-A study, resulting in similar outcomes (median OS of 14.2 vs. 14.7 months). [91] Finally German data further underscored the regimen's survival benefits, with an adjusted hazard ratio for death favoring VEN + HMA (0.48; 95 % CI, 0.29–0.77).

A further alternative for these patients may be the combination of the Hedgehog inhibitor glasdegib with low-dose cytarabine, which has been shown to improve survival compared with low-dose cytarabine alone in a phase II trial. [92,93] Data from clinical practice on glasdegib are limited and show heterogeneous outcomes. A small Italian retrospective study, with 12-month follow-up, reported an ORR of 20 %, with survival not reached in patients achieving any type of response. [94]

With regard to the use of hypomethylating agents (azacitidine and decitabine) in monotherapy, this is usually limited to unfit patients who cannot tolerate the combination with venetoclax, also in absence of targetable mutations. [95] However, the recent approval of an oral formulation of decitabine-cedazuridine for the treatment of adult patients with newly diagnosed AML ineligible for intensive chemotherapy, [96] may result in an increased number of patients treated with this new drug since outpatient or at home care may represent an advantage for patients who cannot easily travel to the hospital for drug administration.

Patients with *IDH1*-mutated AML can be treated with the combination of azacitidine plus ivosidenib (an inhibitor of mutant isocitrate dehydrogenase 1). [6] A phase 3 clinical trial in newly diagnosed patients with *IDH1*-mutated AML, ineligible for IC, showed that the addition of ivosidenib to azacitidine resulted in a significantly longer event-free survival than placebo (HR for treatment failure, relapse from remission, or death, 0.33; 95 %CI 0.16 to 0.69; $p = 0.002$). [97] The combination was also associated with a significantly longer median OS than azacitidine plus placebo (24.0 months versus 7.9 months; HR for death 0.44; 95 %CI 0.27 to 0.73; $p = 0.001$). [97,98]. The clinical benefits of the combination were further supported by a positive impact on HRQoL, increased transfusion independence, and an expected profile of adverse events with fewer neutropenic fever events and infections in patients receiving ivosidenib versus placebo. [97,98] Significant clinical benefits and response rates, a relatively favorable toxicity profile, and ease of administration (once-daily oral dosing) were associated with ivosidenib monotherapy in the subgroup of patients with newly diagnosed, *IDH1*-mutated AML ineligible for standard therapy of a phase I trial. [99] A recent U.S. retrospective chart review focused on IC-ineligible patients with an IDH1 mutation aimed to assess the efficacy and tolerability of combined with HMA compared to venetoclax with HMA as frontline treatments. Results indicate that ivosidenib+HMA may be a viable alternative to VEN + HMA as frontline therapy for IC-ineligible mIDH1 AML patients, regardless of their level of frailty. [100] Additionally, a real-world analysis of Medicare beneficiaries with newly diagnosed IC-ineligible AML explored treatment patterns and clinical outcomes focusing on transfusion independence. This study compared various first-line treatment options, including venetoclax-based regimens and other therapies such as ivosidenib, glasdegib, gilteritinib, enasidenib, midostaurin, and gemtuzumab ozogamicin, highlighting their ability to achieve transfusion independence over time. [101]

5.3. Emerging therapeutic options for patients unfit for intensive chemotherapy

Targeted therapies currently under clinical evaluation include menin inhibitors for AML patients with *KMT2A* rearrangements or *NPM1* mutations. This new class of drugs seems promising and well tolerated in heavily pretreated patients. Menin inhibitors target the *HOX/MEIS1* transcriptional program, crucial for leukemogenesis. These inhibitors disrupt the menin–*KMT2A* complex, leading to differentiation and apoptosis of AML cells with *KMT2A* rearrangements or *NPM1* mutations. Phase I and II clinical trials are ongoing, both as monotherapy and in combination with other drugs, but preliminary data are emerging with force (yet still investigational at the time of this writing). [6,21,102] In the difficult-to-treat setting of *TP53*-mutaded AML, magrolimab (a CD47 inhibitor used in combination with venetoclax and azacitidine) and eprenetapopt (a small-molecule agent that restores *TP53* function) were also investigated. [6,21,102] However, confirmatory phase 3 trials of magrolimab have been discontinued due to lack of clinical advantage [103,104] and in addition to this, the eprenatapopt development program has been recently discontinued. Therefore, patients with *TP53* mutated disease remain a clinical unmet need. Emerging therapies that may play a role in AML with no actionable mutations include inhibitors of the mitotic kinase PLK-1, antibody-drug conjugates (CD33- and CD123-targeted), and immunotherapy (bispecific T-cell engagers andimmune checkpoint inhibitors). [21] Further combinations of hypomethylating agents and small-molecule inhibitors or targeted therapies are under investigation. Triplet therapies, which involve the addition of a third agent (for example, an inhibitor of *FLT3* or *IDH* for patients with *FLT3*- and *IDH*-mutated AML, respectively) to the combination hypomethylating agent-venetoclax, are also raising interest for use in patients ineligible for intensive chemotherapy. [6,21] Finally, the combination of targeted therapy and immunotherapy may potentially lead to chemotherapy-free regimens. [105]

6. Future perspectives

The results of current epidemiologic studies confirm that, with an annual incidence consistently and dramatically increasing after the fifth decade of life, AML is a disease of older adults and that its mortality continues to be high worldwide with a poor prognosis especially in patients aged ≥70 years. Despite significant advances in recent years, long-term survival remains a challenge in patients with AML who are ineligible for induction intensive chemotherapy. These data refer, however, to time periods before the introduction of the recently approved targeted drugs. Hopefully, future epidemiologic data encompassing the new therapeutic strategies will show a further improvement in the outcome of patients with AML.

The new treatment scenario is changing not only patients' outcomes but also the clinical approach that more carefully encompasses a multidisciplinary assessment. An early implementation of a care path involving a team including oncologic-hematologists, geriatricians, cytogeneticists, onco-psychologists, and other specialists depending on patient needs would indeed be a best practice to aim to. This multidisciplinary and certainly multi-level approach could not only allow for the selection of the most suitable therapy with the best outcomes, but it's also expected to reduce the number of patients who are undertreated or not treated at all based exclusively on age or a fitness assessment that does not integrate clinical, biological, and multidimensional measures.

7. Practical considerations and possible future directions

A large body of evidence shows that substantial proportions of patients ineligible for IC do not receive any anti-leukemic therapy and continue therefore to be undertreated. [13,15,16,19,106] Chronological age remains the main factor associated with not being prescribed active treatment, suggesting that many clinicians still predominantly rely on this parameter when making therapeutic decisions. [15] A significant challenge in AML management is represented by disparities in access to drugs and resources, finally impacting therapeutic algorithms across different countries. For instance, while European countries typically provide universal healthcare coverage and broader access to therapies, the U.S. system relies on a mix of private insurance, government programs, and "out-of-pocket" expenses, leading to a higher percentage of untreated patients. Although such information can be extrapolated almost exclusively from studies published between the 1990–2010 decades, the differential access to new drugs across different countries represents a topic of major interest. [13]

Beside country-specific policies of access to drugs, several social factors have been associated to a lower (or higher) probability of active treatment delivery. Several US studies demonstrated an association between female sex, lower household income, and unmarried status and a lower propensity to receive active treatment. [107,108] Moreover, the risk of death among patients with AML seems higher in patients without active support by a caregiver, as well as among Black Americans. [108,109] To counterbalance the effect of such financial and social constraints, future efforts should aim to expand access to novel agents and implement policies that ensure equitable treatment availability. Additionally, comparative studies evaluating treatment access and outcomes between different healthcare systems could provide valuable insights into best practices for improving AML patient management worldwide.

The availability of novel medications and the development of lower-intensity regimens, despite offering new options to otherwise difficult-to-treat patients with AML, are making therapeutic decisions even more complex: the accurate assessment of patients' unfitness/frailness/vulnerability is crucial and needs to take into consideration the new safety profiles. [110] In fact, each regimen yields its own risk/benefit ratio, and the effectiveness of most new strategies is not fully understood. Furthermore, the molecular mutation profile of AML needs to be known when to identify actionable mutations. [110]

Venetoclax-based therapies and ivosidenib plus hypomethylating agent have become the first-line option for newly diagnosed AML patients who are ineligible for IC. [89,111–115] The adoption and utilization of novel therapeutic regimens, particularly outside clinical trial contexts, has led to an extensive real-world data collection over the years. However, these datasets exhibit significant heterogeneity, encompassing retrospective and prospective studies, monocentric versus multicentric designs, and analyses from electronic records and registries, or meta-analyses. This variability affects the interpretation of results and analyzing the amount of publications covered the real world of venetoclax+HMAs, this is quite evident. The creation of prospective, rigorous registries/databases should be encouraged as these tools are crucial for monitoring potential safety issues of venetoclax and other new treatments, as well as their ability to induce CR and impact on quality of life in routine clinical practice [24,63].

Current tools used for evaluating the eligibility of AML patients for intensive chemotherapy may not be sufficiently accurate for evaluating patient eligibility for the newer therapies. In fact, patient fitness for a treatment depends on treatment setting and intensity [66]. Therefore, current fitness scores may need to be adjusted to the new therapies or new treatment-specific tools need to be developed. A recent study involving hematologists from the Italian REL (Rete Ematologica Lombarda) network, with expertise in the treatment of AML with venetoclax-based regimens, investigated about the use of the Ferrara criteria [77]. The study showed that the SIE/SIES/GITMO criteria needs to be adjusted to the candidate patient population for venetoclax based combination including several changes based on their experience and judgement [111]. In detail, a general consensus emerged about including the following additional criteria: age limit 80–85 years, cardiac function >40 %, and absence of recurrent lung infections, bronchiectasis, or exacerbating chronic obstructive pulmonary disease [111]. The experts also indicated the presence of an adequate caregiver as very important in the decision process, to ensure optimal adherence to the scheduled outpatient visits, as well as to closely monitor adverse events.

Recent advances in the field of AML are not only leading to the development of new treatment option but are also changing disease classification [62,65]. The impact of the 2022 updates of AML classification in clinical practice has been addressed in a recent study [44]. The study found that the new classifications improved the accuracy of AML diagnosis compared to the previous classification, as highlighted by the >20 % re-classification of cases that were categorized as "not otherwise specified" according to the 2016 WHO classification [108]. The authors note the increasingly important role of genomic profiling in AML management, and the challenges that this might pose to small centers with no expertise in, or access to, next-generation sequencing (NGS) techniques [116]. In this respect, measures that should be implemented in the near future, to ensure the most suited treatment to each patient, include: improved access to molecular analysis (by NGS); standardization of molecular analysis; creation of referral AML-dedicated centers (with high expertise in NGS-based diagnosis, for example); encourage multidisciplinary collaborations. Notably, the authors also expressed their hope that the two "competing" classifications systems, the WHO 5th edition and the 2022-ICC classification, will be soon fused into a unique system. [44] It is important to highlight that for the first time an attempt was made to adapt genetic risk stratification to patients treated with less intensive regimes. The 2024 ELN Less-Intensive genetic risk classification is applicable in fact to patients receiving either HMA monotherapy, HMA/VEN, or AZA/IVO (for IDH1mut AML).

In conclusion, there is a need for new tools that accurately evaluate patient fitness, including clinical and molecular assessments, to aid a more appropriate choice among novel therapies. Moreover, the management of these new low dose therapies is emerging as a key area of interest with the aim of improving outcomes and balancing efficacy and safety. [117] Finally, the collection of high-quality real-world data could update the missing epidemiological information and highlight the novel

treatments' impact on patient management and outcomes.

8. Research agenda

In the selection of the best treatment option for each patient ineligible for intensive chemotherapy, patient fitness, or patient frailty, should replace patient age. In detail, efforts to ensure/implement the following should be made:

- Adjustment of existing validated fitness scores to new therapies or development and validation of new assessment tools.
- Prospective and structured collection of real-world data about the new therapies to monitor safety and patient outcomes (survival as well as patient-reported outcomes).
- Improve knowledge of the role of genetic analysis in the diagnostic workup of AML, taking into account the importance of genetic risk stratification according to the ELN recommendation published in 2022 and updated in 2024 for patients receiving less intensive therapies.

CRediT authorship contribution statement

Conceptualization: All authors. Methodology and supervision: Ma. CRO Lifescience Srl (funded by AbbVie). Writing – original draft: MaCRO Lifescience Srl, RP. Writing – review and editing: all authors.

Funding

AbbVie funded the project and participated in the design, as well as in interpretation of the data, review, and approval of the manuscript. No honoraria were paid for writing this article.

Declaration of competing interest

Paola Volpicelli, Benedetta Neri, Paola Finsinger and Morena Caira are AbbVie employees and may own AbbVie stocks/options.

Raffaele Palmieri reports Speakers bureau: Abbvie, Janssen, Jazz, Pfizer, Astellas, Novartis, Sobi, Otsuka. Consultant: Janssen, Abbvie, outside the submitted work.

Anna Candoni reports honoraria (consultancy, speaker, advisory role and/or travel support) from AbbVie, Astellas, Janssen, Jazz, Celgene, Gilead, Pfizer, Incyte and Amgen.

Francesco Di Raimondo reports consultancy fee from Pfizer, Amgen, AbbVie, AstraZeneca, Menarini-StemLine; research funding from Jazz Pharmaceuticals; invited speaker fees from Sanofi, AbbVie, Novartis, AstraZeneca, Beigene.

Giuseppe Rossi declares no conflicts of interest.

Massimo Breccia received honoraria by Abbvie, AOP, Novartis, BMS, GSK, Incyte.

Fabrizio Pane declares no conflicts of interest.

Felicetto Ferrara declares no conflicts of interest.

Acknowledgments

The authors wish to thank Lorenza Lanini, on behalf of Ma.CRO Lifescience Srl, for drafting and for editorial support, funded by AbbVie, Giuliana Gualberti and Roberta Cuomo of AbbVie for critical revision and process management.

References

[1] De Kouchkovsky I, Abdul-Hay M. Acute myeloid leukemia: a comprehensive review and 2016 update. Blood Cancer J 2016;6(7):e441.
[2] NCCN. NCCN Clinical Practice Guidelines in Oncology - Acute Myeloid Leukemia. Version 1.2025 — December 20, 2024Version 2.2023. 2024.
[3] Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: recent progress and enduring challenges. Blood Rev 2019;36:70–87.
[4] AIOM. I numeri del cancro in Italia 2022. Available from: https://www.aiom.it/wp-content/uploads/2022/12/2022_AIOM_NDC-web.pdf; 2022.
[5] Juliusson G, Antunovic P, Derolf A, Lehmann S, Möllgård L, Stockelberg D, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute leukemia registry. Blood 2009;113(18):4179–87.
[6] Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood 2022;140(12):1345–77.
[7] EMA. EMA summary of product characteristics - OnuregEMA.
[8] Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE, et al. Age and acute myeloid leukemia. Blood 2006;107(9):3481–5.
[9] EMA. Summary of product characteristics - Gemtuzumab ozogamicinEMA.
[10] EMA. Summary of product characteristics – VyxeosEMA.
[11] de Leeuw DC, Ossenkoppele GJ, Janssen J. Older patients with Acute myeloid leukemia deserve individualized treatment. Curr Oncol Rep 2022;24(11):1387–400.
[12] Hjort Jakobsen L, Stidsholt Roug A, Kiesbye Øvlisen A, Werenberg Marcher C, Beier Ommen H, Theilgaard-Mönch K, et al. Temporal changes in survival among adult patients with acute myeloid leukaemia in the period 2000-2016: a Danish population-based study. Br J Haematol 2021;193(3):482–7.
[13] Hubscher E, Sikirica S, Bell T, Brown A, Welch V, Russell-Smith A, et al. Patterns of undertreatment among patients with acute myeloid leukemia (AML): considerations for patients eligible for non-intensive chemotherapy (NIC). J Cancer Res Clin Oncol 2021;147(11):3359–68.
[14] Huntington SF, Ingham MP, Okonkwo L, Singh A, Wang R, Ammann EM. Treatment patterns, economic burden, and overall survival in US Medicare advantage beneficiaries newly diagnosed with acute myeloid leukemia (AML) in 2015-2020. Leuk Lymphoma 2022;63(5):1180–90.
[15] Li S, Ji Y, Peng Y, Kota V, Kim C. Patient characteristics, treatment patterns, and mortality in elderly patients newly diagnosed with acute myeloid leukemia meeting ineligibility criteria for high intensity chemotherapy. Leuk Lymphoma 2022;63(1):131–41.
[16] Ma E, Bonthapally V, Chawla A, Lefebvre P, Swords R, Lafeuille MH, et al. An evaluation of treatment patterns and outcomes in elderly patients newly diagnosed with Acute myeloid leukemia: a retrospective analysis of electronic medical records from US Community oncology practices. Clin Lymphoma Myeloma Leuk 2016;16(11):625–636.e3.
[17] Martínez-Cuadrón D, Serrano J, Gil C, Tormo M, Martínez-Sánchez P, Pérez-Simón JA, et al. Evolving treatment patterns and outcomes in older patients (≥60 years) with AML: changing everything to change nothing? Leukemia 2021;35(6):1571–85.
[18] Medeiros BC, Satram-Hoang S, Hurst D, Hoang KQ, Momin F, Reyes C. Big data analysis of treatment patterns and outcomes among elderly acute myeloid leukemia patients in the United States. Ann Hematol 2015;94(7):1127–38.
[19] Miyamoto T, Sanford D, Tomuleasa C, Hsiao HH, Olivera LJE, Enjeti AK, et al. Real-world treatment patterns and clinical outcomes in patients with AML unfit for first-line intensive chemotherapy. Leuk Lymphoma 2022;63(4):928–38.
[20] Talati C, Dhulipala VC, Extermann MT, Ali NA, Kim J, Komrokji R, et al. Comparisons of commonly used front-line regimens on survival outcomes in patients aged 70 years and older with acute myeloid leukemia. Haematologica 2020;105(2):398–406.
[21] Choi JH, Shukla M, Abdul-Hay M. Acute myeloid leukemia treatment in the elderly: a comprehensive review of the present and future. Acta Haematol 2023;146(6):431–57.
[22] Beckmann K, Kearney BA, Yeung D, Hiwase D, Li M, Roder DM. Changes in five-year survival for people with acute leukaemia in South Australia, 1980-2016. Med J Aust 2022;216(6):296–302.
[23] Roman E, Smith A, Appleton S, Crouch S, Kelly R, Kinsey S, et al. Myeloid malignancies in the real-world: occurrence, progression and survival in the UK'S population-based Haematological malignancy research network 2004-15. Cancer Epidemiol 2016;42:186–98.
[24] Calabria S, Ronconi G, Dondi L, Piccinni C, Pedrini A, Esposito I, et al. Acute myeloid leukemia: incidence, transplantation and survival through Italian administrative healthcare data. Tumori 2023;109(5):496–503.
[25] Fuji S, Kida S, Nakata K, Morishima T, Miyashiro I, Ishikawa J. Long-term trends in the clinical outcomes of patients with acute myeloid leukemia: a population-based real-world data analysis using the Osaka Cancer registry. Ann Hematol 2021;100(11):2717–25.
[26] Gangatharan SA, Grove CS, P'ng S, O'Reilly J, Joske D, Leahy MF, et al. Acute myeloid leukaemia in Western Australia 1991-2005: a retrospective population-based study of 898 patients regarding epidemiology, cytogenetics, treatment and outcome. Intern Med J 2013;43(8):903–11.
[27] Granfeldt Østgård LS, Medeiros BC, Sengeløv H, Nørgaard M, Andersen MK, Dufva IH, et al. Epidemiology and clinical significance of secondary and therapy-related Acute myeloid leukemia: a National Population-Based Cohort Study. J Clin Oncol 2015;33(31):3641–9.
[28] McGregor AK, Moulton D, Bown N, Cuthbert G, Bourn D, Mathew S, et al. Incidence and outcomes for adults diagnosed with acute myeloid leukemia in the north of England: a real world study. Leuk Lymphoma 2016;57(7):1575–84.
[29] Bassig BA, Hu W, Morton LM, Ji BT, Xu J, Linet MS, et al. Incidence of myeloid malignancies by subtype in Hong Kong and comparisons with Asian and white men and women in the United States. Leuk Lymphoma 2022;63(8):1917–24.

[30] Broccia G, Deplano W, Dessalvi P, Giannico B, Luxi G, Chessa E, et al. Hematological malignancies in the island of Sardinia, 1974-1993: age and sex distributions and temporal changes in incidence. Hematol Oncol 2004;22(3):91–109.
[31] Busco S, Buzzoni C, Mallone S, Trama A, Castaing M, Bella F, et al. Italian cancer figures–Report 2015: The burden of rare cancers in Italy. Epidemiol Prev 2016;40 (1 Suppl 2):1–120.
[32] Shysh AC, Nguyen LT, Guo M, Vaska M, Naugler C, Rashid-Kolvear F. The incidence of acute myeloid leukemia in Calgary, Alberta, Canada: a retrospective cohort study. BMC Public Health 2017;18(1):94.
[33] Solans M, Sanvisens A, Ameijide A, Merino S, Rojas D, Alemán A, et al. Incidence of myeloid neoplasms in Spain (2002−2013): a population-based study of the Spanish network of cancer registries. Sci Rep 2022;12(1):323.
[34] Pulsoni A, Pagano L, Latagliata R, Casini M, Cerri R, Crugnola M, et al. Survival of elderly patients with acute myeloid leukemia. Haematologica 2004;89(3):296–302.
[35] Turbeville S, Francis KM, Behm I, Chiu GR, Sanchez H, Morrison BA, et al. Prevalence and incidence of Acute myeloid leukemia may be higher than currently accepted estimates among the ≥65 year-old population in the United States. Blood 2014;124(21):958.
[36] Dong Y, Shi O, Zeng Q, Lu X, Wang W, Li Y, et al. Leukemia incidence trends at the global, regional, and national level between 1990 and 2017. Exp Hematol Oncol 2020;9:14.
[37] Ocias LF, Larsen TS, Vestergaard H, Friis LS, Abildgaard N, Frederiksen H. Trends in hematological cancer in the elderly in Denmark, 1980-2012. Acta Oncol 2016;55(Suppl. 1):98–107.
[38] Chien LN, Tzeng HE, Liu HY, Chou WC, Tien HF, Hou HA. Epidemiology and survival outcomes of acute myeloid leukemia patients in Taiwan: a national population-based analysis from 2001 to 2015. J Formos Med Assoc 2023;122(6):505–13.
[39] Coviello V, Buzzoni C, Fusco M, Barchielli A, Cuccaro F, De Angelis R, et al. Survival of cancer patients in Italy. Epidemiol Prev 2017;41(2 Suppl 1):1–244.
[40] Philip C, George B, Ganapule A, Korula A, Jain P, Alex AA, et al. Acute myeloid leukaemia: challenges and real world data from India. Br J Haematol 2015;170 (1):110–7.
[41] Juliusson G, Hagberg O, Lazarevic VL, Ölander E, Antunovic P, Cammenga J, et al. Improved survival of men 50 to 75 years old with acute myeloid leukemia over a 20-year period. Blood 2019;134:1558–61.
[42] Sant M, Minicozzi P, Mounier M, Anderson LA, Brenner H, Holleczek B, et al. Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. Lancet Oncol 2014;15(9):931–42.
[43] Schnegg-Kaufmann A, Feller A, Baldomero H, Rovo A, Manz MG, Gregor M, et al. Improvement of relative survival in elderly patients with acute myeloid leukaemia emerging from population-based cancer registries in Switzerland between 2001 and 2013. Cancer Epidemiol 2018;52:55–62.
[44] Attardi E, Savi A, Borsellino B, Piciocchi A, Cipriani M, Ottone T, et al. Applicability of 2022 classifications of acute myeloid leukemia in the real-world setting. Blood Adv 2023;7(17):5122–31.
[45] Lerch E, Espeli V, Zucca E, Leoncini L, Scali G, Mora O, et al. Prognosis of acute myeloid leukemia in the general population: data from southern Switzerland. Tumori 2009;95(3):303–10.
[46] Juliusson G, Abrahamsson J, Lazarevic V, Antunovic P, Derolf Å, Garelius H, et al. Prevalence and characteristics of survivors from acute myeloid leukemia in Sweden. Leukemia 2017;31:728–31.
[47] Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010;116(19):3724–34.
[48] Visser O, Trama A, Maynadié M, Stiller C, Marcos-Gragera R, De Angelis R, et al. Incidence, survival and prevalence of myeloid malignancies in Europe. Eur J Cancer 2012;48(17):3257–66.
[49] Song X, Peng Y, Wang X, Chen Y, Jin L, Yang T, et al. Incidence, survival, and risk factors for adults with Acute myeloid leukemia not otherwise specified and Acute myeloid leukemia with recurrent genetic abnormalities: analysis of the surveillance, epidemiology, and end results (SEER) database, 2001-2013. Acta Haematol 2018;139(2):115–27.
[50] Ghazawi FM, Le M, Cyr J, Netchiporouk E, Rahme E, Alakel A, et al. Analysis of acute myeloid leukemia incidence and geographic distribution in Canada from 1992 to 2010 reveals disease clusters in Sarnia and other industrial US border cities in Ontario. Cancer 2019;125(11):1886–97.
[51] Capra M, Vilella L, Pereira WV, Coser VM, Fernandes MS, Schilling MA, et al. Estimated number of cases, regional distribution and survival of patients diagnosed with acute myeloid leukemia between 1996 and 2000 in Rio Grande do Sul, Brazil. Leuk Lymphoma 2007;48(12):2381–6.
[52] Bekadja MA, Hamladji RM, Belhani M, Ardjoun FZ, Abad MT, Touhami H, et al. A population-based study of the epidemiology and clinical features of adults with acute myeloid leukemia in Algeria: report on behalf of the Algerian Acute leukemia study group. Hematol Oncol Stem Cell Ther 2011;4(4):161–6.
[53] Oelofse D, Truter I. Incidence of haematological malignancies, eastern Cape Province; South Africa, 2004-2013. Cancer Epidemiol 2018;53:166–71.
[54] Matsunaga T, Yamashita K, Kubuki Y, Toyama T, Imataki O, Maeda K, et al. Acute myeloid leukemia in clinical practice: a retrospective population-based cohort study in Miyazaki prefecture, Japan. Int J Hematol 2012;96(3):342–9.
[55] Huang HH, Chen CM, Wang CY, Hsu WW, Chen HM, Ko BS, et al. The epidemiology, treatment patterns, healthcare utilizations and costs of Acute myeloid Leukaemia (AML) in Taiwan. PLoS One 2022;17(1):e0261871.
[56] Wanitpongpun C, Utchariyaprasit E, Owattanapanich W, Tantiworawit A, Rattarittamrong E, Niparuck P, et al. Types, clinical features, and survival outcomes of patients with Acute myeloid leukemia in Thailand: a 3-year prospective multicenter study from the Thai Acute leukemia study group (TALSG). Clin Lymphoma Myeloma Leuk 2021;21(7):e635–43.
[57] Alshemmari SH, Almazyad M, Ram M, John LM, Alhuraiji A. Epidemiology of de novo Acute myeloid leukemia in Kuwait per the 2016 WHO classification. Med Princ Pract 2022;31(3):284–92.
[58] Aitbekov R, Murzakhmetova M, Zhamanbayeva G, Zhaparkulova N, Seel H. Epidemiological features of Acute myeloid leukemia in five regions of the Republic of Kazakhstan: population study. Asian Pac J Cancer Prev 2022;23(12):4163–7.
[59] Khondkaryan L, Andreasyan D, Hakobyan Y, Bankoglu EE, Aroutiounian R, Stopper H, et al. Incidence and risk factors of Acute Leukemias in Armenia: a population-based study. Asian Pac J Cancer Prev 2022;23(11):3869–75.
[60] Morice PM, Leary A, Dolladille C, Chrétien B, Poulain L, González-Martín A, et al. Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol 2021;8(2):e122–34.
[61] Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391–405.
[62] Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of Haematolymphoid Tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36(7):1703–19.
[63] Palmieri R, Paterno G, De Bellis E, Mercante L, Buzzatti E, Esposito F, et al. Therapeutic choice in older patients with Acute myeloid leukemia: a matter of fitness. Cancers 2020;12(1).
[64] Dohner H, DiNardo CD, Wei AH, Lowenberg B, Appelbaum F, Craddock C, et al. Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. Blood 2024;144(21):2169–73.
[65] Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, et al. International consensus classification of myeloid neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood 2022;140 (11):1200–28.
[66] Bhatt VR, Uy GL, Klepin HD. Determining treatment tolerance and fitness for intensive chemotherapy in older adults with AML: a call to action. Blood 2024;143(6):483–7.
[67] Venditti A, Palmieri R, Maurillo L, Röllig C, Wierzbowska A, de Leeuw DC, et al. Fitness assessment in acute myeloid leukemia: recommendations from an expert panel on behalf of European leukemia net. Blood Adv 2025:2024013744. Online ahead of print.
[68] Venditti A, Cairoli R, Caira M, Finsinger P, Finocchiaro F, Neri B, et al. Assessing eligibility for treatment in acute myeloid leukemia in 2023. Expert Rev Hematol 2023;16(3):181–90.
[69] Lancet JE, Willman CL, Bennett JM. Acute myelogenous leukemia and aging. Clinical interactions. Hematol Oncol Clin North Am 2000;14(1):251–67.
[70] Bacher U, Kern W, Schnittger S, Hiddemann W, Haferlach T, Schoch C. Population-based age-specific incidences of cytogenetic subgroups of acute myeloid leukemia. Haematologica 2005;90(11):1502–10.
[71] Loprinzi CL, Laurie JA, Wieand HS, Krook JE, Novotny PJ, Kugler JW, et al. Prospective evaluation of prognostic variables from patient-completed questionnaires. North central Cancer treatment group. J Clin Oncol 1994;12(3):601–7.
[72] Kadia TM, Cortes J, Ravandi F, Jabbour E, Konopleva M, Benton CB, et al. Cladribine and low-dose cytarabine alternating with decitabine as front-line therapy for elderly patients with acute myeloid leukaemia: a phase 2 single-arm trial. Lancet Haematol 2018;5(9):e411–21.
[73] Michaelis LC, Klepin HD, Walter RB. Advancements in the management of medically less-fit and older adults with newly diagnosed acute myeloid leukemia. Expert Opin Pharmacother 2018;19(8):865–82.
[74] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.
[75] Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Pardee TS, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood 2013;121(21):4287–94.
[76] Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Ellis LR, et al. The feasibility of inpatient geriatric assessment for older adults receiving induction chemotherapy for acute myelogenous leukemia. J Am Geriatr Soc 2011;59(10):1837–46.
[77] Ferrara F, Barosi G, Venditti A, Angelucci E, Gobbi M, Pane F, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. Leukemia 2013;27:997–9.
[78] Sorror ML, Storer BE, Fathi AT, Brunner A, Gerds AT, Sekeres MA, et al. Multisite 11-year experience of less-intensive vs intensive therapies in acute myeloid leukemia. Blood 2021;138(5):387–400.
[79] Walter RB, Othus M, Borthakur G, Ravandi F, Cortes JE, Pierce SA, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. J Clin Oncol 2011;29(33):4417–23.
[80] Borlenghi E, Pagani C, Zappasodi P, Bernardi M, Basilico C, Cairoli R, et al. Validation of the "fitness criteria" for the treatment of older patients with acute

myeloid leukemia: a multicenter study on a series of 699 patients by the network rete Ematologica Lombarda (REL). J Geriatr Oncol 2021;12(4):550–6.
[81] Palmieri R, Paterno G, De Bellis E, Buzzatti E, Rossi V, Di Veroli A, et al. Validation of SIE, Sies, GITMO operational criteria for the definition of fitness in elderly patients affected with acute myeloid leukemia: a six-years retrospective real-life experience. Blood 2019;134:2150.
[82] Palmieri R, Othus M, Halpern AB, Percival MM, Godwin CD, Becker PS, et al. Accuracy of SIE/SIES/GITMO consensus criteria for unfitness to predict early mortality after intensive chemotherapy in adults with AML or other high-grade myeloid neoplasm. J Clin Oncol 2020;38(35):4163–74.
[83] DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in previously untreated Acute myeloid leukemia. N Engl J Med 2020;383(7):617–29.
[84] Pratz KW, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Döhner H, et al. Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. Am J Hematol 2024;99(4):615–24.
[85] Pratz KW, Panayiotidis P, Recher C, Wei X, Jonas BA, Montesinos P, et al. Venetoclax combinations delay the time to deterioration of HRQoL in unfit patients with acute myeloid leukemia. Blood Cancer J 2022;12(4):71.
[86] DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 2019;133(1):7–17.
[87] Wei AH, Montesinos P, Ivanov V, DiNardo CD, Novak J, Laribi K, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. Blood 2020;135(24):2137–45.
[88] Hoff FW, Patel PA, Belli AJ, Hansen E, Foss H, Schulte M, et al. Real-world outcomes of frontline venetoclax-based therapy in older adults with acute myeloid leukemia: an analysis utilizing EHR data. Leuk Lymphoma 2023;64(6):1123–8. https://doi.org/10.1080/10428194.2023.2197090.
[89] Ucciero A, Pagnoni F, Scotti L, Pisterna A, Barone-Adesi F, Gaidano G, et al. Venetoclax with Hypomethylating agents in newly diagnosed Acute myeloid leukemia: a systematic review and Meta-analysis of survival data from real-world studies. Cancers 2023;15(18):4618.
[90] Abaza Y, Winer ES, Murthy GSG, Shallis RM, Matthews AH, Badar T, et al. Clinical outcomes of hypomethylating agents plus Venetoclax as frontline treatment in patients 75 years and older with acute myeloid leukemia: real-world data from eight US academic centers. Am J Hematol 2024;99(4):606–14. https://doi.org/10.1002/ajh.27231.
[91] Venditti A, Piciocchi A, Soddu S, Frigeni M, Palmieri R, Borlenghi E, et al. Real world outcome of unfit patients with Acute myeloid leukemia treated with the combination Venetoclax plus Hypomethylating agents in the Gimema AML2320 observational trial. Blood 2023;142:1514.
[92] Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia 2019;33(2):379–89.
[93] Heuser M, Smith BD, Fiedler W, Sekeres MA, Montesinos P, Leber B, et al. Clinical benefit of glasdegib plus low-dose cytarabine in patients with de novo and secondary acute myeloid leukemia: long-term analysis of a phase II randomized trial. Ann Hematol 2021;100(5):1181–94.
[94] Tanasi I, Bruzzese A, Di Veroli A, Vetro C, Rizzo L, De Luca G, et al. Association of Glasdegib+ low-dose Cytarabine (AraC) in the real-life treatment of very frail elderly Acute myeloid Leukemias (AML) patients. Blood 2024;144:6041.
[95] SIE. Società Italiana di Ematologia. Linee guida. Leucemia acuta mieloide non promielocitica nel paziente >= 60 anni. Available from: https://www.siematologia.it/linee-guida-sie.html; 2023.
[96] EMA. Product overview – Inaqovi EMA.
[97] Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, et al. Ivosidenib and Azacitidine in IDH1-mutated Acute myeloid leukemia. N Engl J Med 2022;386(16):1519–31.
[98] De Botton S, Montesinos P, Vives Polo S, Zarzycka E, Wang J, Riva M, et al. Updated efficacy and safety data from the AGILE study in patients with newly diagnosed acute myeloid leukemia treated with ivosidenib + azacitidine compared to placebo + azacitidine. 2023. https://doi.org/10.1200/JCO.2023.41.16_suppl.7012.
[99] Roboz GJ, DiNardo CD, Stein EM, de Botton S, Mims AS, Prince GT, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. Blood 2020;135(7):463–71.
[100] Smith BD, Lachowiez CA, Ambinder AJ, Binder G, Angiolillo A, Potluri R, et al. Outcomes by frailty in IC-ineligible newly diagnosed AML-a real-world evidence comparison by treatment with Hypomethylating agents+ Ivosidenib or Venetoclax. Blood 2024;144:2855.
[101] Zeidan AM, Cheng WH, Kamalakar R, Miller C, Bui CN, Montez M, et al. Real-world treatment patterns and transfusion burden among newly diagnosed older adults with Acute myeloid leukemia. Blood 2022;140(Supplement 1):3282–3.
[102] Oyogoa E, Traer E, Tyner J, Lachowiez C. Building on foundations: Venetoclax-based combinations in the treatment of Acute myeloid leukemia. Cancers (Basel) 2023;15(14).
[103] CancerNetwork. FDA places full clinical hold on magrolimab trials in AML-MDS. Available from: https://www.cancernetwork.com/view/fda-places-full-clinical-hold-on-magrolimab-trials-in-aml-mds; 2024.
[104] OncLive. Gilead discontinues phase 3 ENHANCE 2 trial of magrolimab plus azacitidine in TP53-mutant AML. 2023.
[105] Blum WG, Mims AS. Treating acute myeloid leukemia in the modern era: a primer. Cancer 2020;126(21):4668–77.
[106] Dharmani C, Wang E, Tu N, Fofah O, Cueto J, Salas M, et al. Elderly patients with acute myeloid leukemia who only receive supportive care in the surveillance, epidemiology and end results-Medicare database: demographics, treatment patterns and outcomes. Future Oncol 2023;19(24):1677–93.
[107] Byrne MM, Halman LJ, Koniaris LG, Cassileth PA, Rosenblatt JD, Cheung MC. Effects of poverty and race on outcomes in acute myeloid leukemia. Am J Clin Oncol 2011;34(3):297–304. https://doi.org/10.1097/COC.0b013e3181dea934 [PMID: 20562587].
[108] Costa LJ, Brill IK, Brown EE. Impact of marital status, insurance status, income, and race/ethnicity on the survival of younger patients diagnosed with multiple myeloma in the United States. Cancer 2016;122(20):3183–90. https://doi.org/10.1002/cncr.30183.
[109] Goyal G, Nawal L, Mosalpuria K, Silberstein PT. Impact of socioeconomic, demographic and health system factors on therapy in acute myeloid leukemia. Blood 2015;126(23):3316.
[110] Diekmann B, Timmerman M, Hempenius L, van Roon E, Franken B, Hoogendoorn M. New treatment opportunities for older patients with acute myeloid leukemia and the increasing importance of frailty assessment - an oncogeriatric perspective. J Geriatr Oncol 2024;15(2):101631.
[111] Rossi G, Borlenghi E, Zappasodi P, Lussana F, Bernardi M, Basilico C, et al. Adapting the fitness criteria for non-intensive treatments in older patients with Acute myeloid leukemia to the use of Venetoclax-Hypomethylating agents combination-practical considerations from the real-life experience of the hematologists of the rete Ematologica Lombarda. Cancers 2024;16(2).
[112] Martinez-Cuadron D, Boluda B, Algarra JL, Bergua Burgues JM, Rodriguez Veiga R, Martinez Sanchez P, et al. Treatment outcomes in unfit patients with newly Acute myeloid leukemia according to IDH1 mutational status: real world evidence from the Pethema epidemiologic registry. Blood 2023;142:4223.
[113] Matthews AH, Perl AE, Luger SM, Gill SI, Lai C, Porter DL, et al. Real-world effectiveness of intensive chemotherapy with 7&3 versus venetoclax and hypomethylating agent in acute myeloid leukemia. Am J Hematol 2023;98(8):1254–64.
[114] Matthews AH, Perl AE, Luger SM, Loren AW, Gill SI, Porter DL, et al. Real-world effectiveness of CPX-351 vs venetoclax and azacitidine in acute myeloid leukemia. Blood Adv 2022;6(13):3997–4005.
[115] Smith BD, Lachowiez CA, Ambinder AJ, Binder G, Angiolillo A, Vestin A, et al. A comparison of Acute myeloid leukemia (AML) regimens: Hypomethylating agents combined with Ivosidenib or Venetoclax in newly diagnosed patients with IDH1 mutations: a real-world evidence study. Blood 2023;142:971.
[116] Duncavage EJ, Bagg A, Hasserjian RP, DiNardo CD, Godley LA, Iacobucci I, et al. Genomic profiling for clinical decision making in myeloid neoplasms and acute leukemia. Blood 2022;140(21):2228–47.
[117] Sastow D, Levavi H, Wagner N, Pratz K, Tremblay D. Ven the dose matters: Venetoclax dosing in the frontline treatment of AML. Blood Rev 2024;68:101238. https://doi.org/10.1016/j.blre.2024.101238.