Venetoclax plus decitabine as a bridge to allogeneic haematopoietic stem-cell transplantation in older patients with acute myeloid leukaemia (VEN-DEC GITMO): final report of a multicentre, single-arm, phase 2 trial

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Summary

Background Access to allogeneic haematopoietic stem-cell transplantation (HSCT) remains challenging for older patients (aged >60 years) with acute myeloid leukaemia. We aimed to evaluate the efficacy of venetoclax plus decitabine as first-line therapy and bridge to transplantation in this patient population.

Methods This multicentre, single-arm, phase 2 trial was conducted in 20 Gruppo Italiano Trapianto Midollo Osseo (GITMO) centres in Italy. Patients aged ≥60 and <75 years, with newly diagnosed acute myeloid leukaemia categorised as intermediate or high risk according to 2016 WHO and 2017 European LeukemiaNet, an ECOG performance status of less than 2, and considered fit for allogeneic HSCT were included. Patients received oral venetoclax with a 3-day ramp-up: 100 mg on day 1, 200 mg on day 2, and 400 mg once per day from day 3 of cycle one, and then every 28 days of each cycle (two to four in total). Decitabine was administered intravenously at a dose of 20 mg/m² from days 1 to 5 every 28 days. At cycle one, patients were admitted to hospital for a minimum of 24 h, whereas subsequent cycles could be administered on an outpatient basis. Two additional cycles were allowed while waiting for allogeneic HSCT or for those with no response or partial response after cycle two. The primary endpoint was the proportion of patients who had allogeneic HSCT performed during first complete remission, assessed in all patients who received at least one dose of the study medication. This study was registered with ClinicalTrials.gov (NCT04476199, ongoing) and EudraCT (2020–002297–26).

Findings Between June 1, 2021, and Dec 30, 2022, 93 patients were enrolled and started venetoclax plus decitabine induction (44 [47%] at intermediate risk and 49 [53%] at high risk). The median age was 68·5 (IQR 60·3–74·7). All 93 participants were White, of whom 43 (46%) were female and 50 (54%) were male. The median follow-up was 236 days (IQR 121–506). 64 (69%) of 93 patients reached complete remission and 53 (57%) underwent allogeneic HSCT in complete remission. 53 (83%) of 64 with a complete remission underwent allogeneic HSCT. Five (8%) of 64 patients in complete remission relapsed before transplantation and four died as a consequence. Adverse events (grade ≥3) occurred in 49 (53%) of 93 patients. The most common adverse events were infections (including pneumonia, bacterial sepsis, and SARS-CoV-2 causing seven deaths among 28 [57%] of 49 patients), neutropenia (17 [35%]), thrombocytopenia (two [4%], including one fatal CNS bleeding), and cardiac events (four [8%], including one fatal heart failure). No treatment-related deaths were observed.

Interpretation Venetoclax plus decitabine induction can significantly enhance the feasibility of allogeneic HSCT in older patients with acute myeloid leukaemia who are deemed fit for transplantation.

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Introduction

Acute myeloid leukaemia therapy has remained unchanged in the past 50 years and continues to be an unmet clinical need, especially for older people (aged >60 years).[1] 60–80% of patients younger than 60 years reaching complete remission can obtain long-term overall survival with the extensive use of allogeneic haematopoietic stem-cell transplantation (HSCT) during the first complete remission.[2] This progress has not been extended to older patients, mainly because of the low use of allogeneic HSCT,[3] and outcomes are bleaker than those observed in younger

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Research in context

Evidence before this study

We searched PubMed for articles published from Jan 1, 2000, to May 10, 2024. Using the search terms: "acute myeloid leukaemia", "older", and "intensive induction chemotherapy", we found 292 articles. When we considered the search terms: "venetoclax" AND/OR "decitabine", "complete remission allogeneic stem cell transplantation", "transplant rate", and "transplant outcomes", we found 21 articles. The literature showed a reduced rate of complete remission and access to allogeneic haematopoietic stem cell transplantation in patients older than 60 years across different studies. Venetoclax in combination with hypomethylating agents, such as azacitidine or decitabine, have shown to induce complete remission in 60–70% of patients. However, this combination is authorised as first-line therapy only in older or frail patients with acute myeloid leukaemia and is not suitable as induction in older patients considered fit for allogeneic HSCT.

Added value of this study

Our study presents a new scenario in the treatment strategy for older patients with acute myeloid leukaemia who are eligible for transplantation. Venetoclax plus decitabine induction not only has shown to induce a high rate of complete remission, but also to preserve the patients' clinical fitness and serve as a bridge to allogeneic HSCT. Our data emphasise the fast anti-acute myeloid leukaemia effect of venetoclax plus decitabine, the low rate of disease recurrence (even within a high-risk population), and the safety of this combination allowing most patients to continue treatment in an outpatient setting, which could possibility reduce the costs associated with longer hospital stay for intensive chemotherapy.

Implications of all the available evidence

According to the latest 2022 European LeukemiaNet recommendations, older patients with acute myeloid leukaemia considered suitable for transplantation should undergo an anthracycline-containing induction and consolidation regimen to reach complete remission. Despite reaching complete remission in around 50% of patients, less than 10–15% who receive anthracycline-containing induction can undergo allogeneic HSCT due to therapy-related toxic effects, worsening of comorbidities, or delayed referral to transplant centres. Our data appear to outperform previous reports, in which the percentage of older patients with acute myeloid leukaemia who received transplantation was around 15–18%. Our study might effectively change the current clinical practise and would mark an important turning point in designing the therapeutic strategy for patients older than 60 years with acute myeloid leukaemia. Further validation is required, but this study can inspire future research on new induction treatments for older and younger patients.

people with an expected complete remission rate of less than 50% and an overall survival of less than 10–15%, even in those patients considered fit for intensive chemotherapies.[3] In 2020, Gardin and colleagues reported a complete remission rate of 72% but an allogeneic HSCT rate of 18%.[4]

The access to allogeneic HSCT still remains a challenge for patients older than 60 years with acute myeloid leukaemia. Less than 10% of these patients will undergo allogeneic HSCT due to several factors, such as an inadequate complete response to induction, therapy-related toxic effects, comorbidities, or delayed referral to transplant centres.[5] In this setting, hypomethylating agents have shown a better response rate leading to allogeneic HSCT rates of up to 40%.[6]

The combination of venetoclax with hypomethylating agents has shown to induce complete remission in around 60–70% of older or frail patients with acute myeloid leukaemia and a low toxicity.[7] However, this combination is authorised as first-line therapy only in elderly or frail patients with acute myeloid leukaemia who are not suitable for intensive induction and consolidation chemotherapies.[8]

Based on these premises, we aimed to evaluate the activity of venetoclax plus decitabine combination as first-line therapy in fit older patients with acute myeloid leukaemia as a bridge to transplantation.

Methods

Study design and participants

This multicentre, single-arm, phase 2 trial was conducted in 20 Gruppo Italiano Trapianto Midollo Osseo (GITMO) centres in Italy. Patients with newly diagnosed acute myeloid leukaemia (aged ≥60 and <75 years) categorised as intermediate or high risk according to 2016 WHO[9] and 2017 European LeukemiaNet (ELN)[10] classifications, with an ECOG performance status less than 2, and considered fit for allogeneic HSCT were included. Patients also had to have a white blood cell count of less than 25×10^9 cells/L (the use of hydroxyurea was allowed to reach this criterion), adequate hepatic function (bilirubin ≤2 times upper limit of normal [ULN]; aspartate aminotransferase to alanine transaminase ratio ≤2·5 times ULN), and adequate renal function (creatinine clearance ≥50 mL/min). To ascertain the diagnostic and risk distribution, patients were then reclassified by the newest 2022 WHO[11] and ELN[1] classifications (appendix pp 3–4).

Patients who had previous treatment for acute myeloid leukaemia (excluding hydroxyurea) or for antecedent myelodysplastic syndromes; those with t(15;17), t(8;21), or inv(16); CNS involvement, serious organ dysfunction, or low-risk disease as per 2017 ELN criteria; evidence of active HBV or HCV infection or other uncontrolled infections; HIV; other life-threatening concurrent disease or a history of other malignancies within 2 years before

study entry; and grade 2 or worse adverse events at the time of enrolment were excluded.

The local ethics committee approved the study protocol, and all patients provided written informed consent. The trial adhered to the Declaration of Helsinki. A list of centres and patients recruited can be found in the appendix (p 20). This study was registered with ClinicalTrials.gov (NCT04476199, ongoing) and EudraCT (2020–002297–26).

Procedures

Patients received oral venetoclax with a 3-day ramp-up: 100 mg on day 1, 200 mg on day 2, and 400 mg once per day from day 3 of cycle one, and then every 28 days of each cycle. Decitabine was administered intravenously at a dose of 20 mg/m² from days 1 to 5 every 28 days.

At cycle one, patients were admitted to hospital for a minimum of 24 h, whereas subsequent cycles could be administered on an outpatient basis. The venetoclax dose was adjusted when concurrent moderate or strong CYP3A inhibitors were administered (appendix p 5). Venetoclax and decitabine could be dose-adjusted or delayed in case of haematological toxic effects or justified clinical or laboratory causes.

Response evaluation, using ELN criteria,[10] was due after the second induction cycle upon discontinuation of venetoclax. In cases of complete remission, complete remission with incomplete haematological recovery, or morphological leukaemia-free state, patients were required to undergo allogeneic HSCT, preferably within 2 months since response evaluation. Two additional venetoclax plus decitabine cycles were allowed while waiting for allogeneic HSCT or for those with no response or partial response after cycle two. Patients with no response or partial response after cycle four were discontinued from the study. Treatment was discontinued in case of severe adverse events, non-compliance, or withdrawal of consent.

Adverse events were monitored once or three times a week until allogeneic HSCT. Treatment-related adverse events were defined in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5). Granulocyte colony-stimulating factor was allowed during induction therapy in case of febrile neutropenia.

Biological characterisation of acute myeloid leukaemia and monitoring of measurable residual disease (MRD) were conducted locally using flow cytometry, cytogenetics, and RT-PCR (RT-qPCR) targeting specific genes (*FLT3-ITD*, *NPM1A*, and *FLT3-TKD* mutations and *WT1* expression).[12,13] The genomic analysis was done using a next-generation sequencing (NGS) panel (Sophia Genetics, Lausanne, Switzerland) and centralised in the Brescia CREA-Laboratory (Brescia, Italy; appendix pp 1–2).[14,15]

Outcomes

The primary endpoint was the proportion of patients who had allogeneic HSCT performed during first complete remission (including complete remission, complete remission with incomplete haematological recovery, and morphological leukaemia-free state) after venetoclax plus decitabine induction.

Secondary endpoints included the cumulative incidence of graft failure at 30 and 100 days after transplantation; non-relapse mortality at day 100, 1 year, and 2 years after allogeneic HSCT; cumulative incidence and severity of acute graft-versus-host disease (GVHD) at 100 days after transplantation; cumulative incidence and severity of chronic GVHD, overall survival, disease-free survival, GVHD relapse-free survival; relapse incidence at 1 and 2 years after allogeneic HSCT; incidence and severity of adverse events; and the correlation of immunophenotype, cytogenetic, molecular, and NGS genomic profiles with sensitivity (complete remission, complete remission with incomplete haematological recovery, and morphological leukaemia-free state) or resistance (partial response, no response) to venetoclax plus decitabine, and with the outcomes of allogeneic HSCT, including non-relapse mortality, relapse incidence, disease-free survival, and overall survival.

Statistical analysis

We aimed to enrol 100 patients with an assumption that 60–70% of patients receiving venetoclax plus decitabine would reach complete remission, compared with 30–40% of those receiving standard chemotherapy. We expected that around 50–70% (ie, 30–40) patients in complete remission would be eligible for allogeneic HSCT because of donor availability and clinical conditions.

Considering the existing literature indicating that fewer than 10% of older patients (aged between ≥60 and <75 years) with acute myeloid leukaemia reach the goal allogeneic HSCT, primarily due to no response or partial response to conventional chemotherapy or treatment-related toxicity (or both), the null hypothesis was tested (conventional chemotherapy with $p \leq 0 \cdot 10$) against the alternative (venetoclax plus decitabine with $p \geq 0 \cdot 20$). The expected sample size was 89 patients, with a probability of early termination of $0 \cdot 647$, when true proportion is $0 \cdot 1$. The α error was $0 \cdot 048$ and β error was $0 \cdot 198$. The null hypothesis will be rejected if 14 or more treated patients receive allogeneic HSCT.

According to Simon's two-stage design, a planned futility check (ie, interim analysis) was set after the first 30 patients and in case of three or fewer transplanted patients, the trial would have been stopped for inefficacy (appendix p 1). By March 30, 2022, the trial had reached the required number of patients for the interim analysis and five patients had already undergone transplantation during complete remission, thus obviating the need for accrual suspension. Accrual continued as planned until Dec 30, 2022, considering an overall 12% dropout rate, 70 additional patients will be accrued for 100 enrolled patients.

Efficacy and safety were assessed in all patients who received at least one therapeutic dose of study medication.

See **Online** for appendix

For the **study registry** see https://clinicaltrials.gov/study/NCT04476199

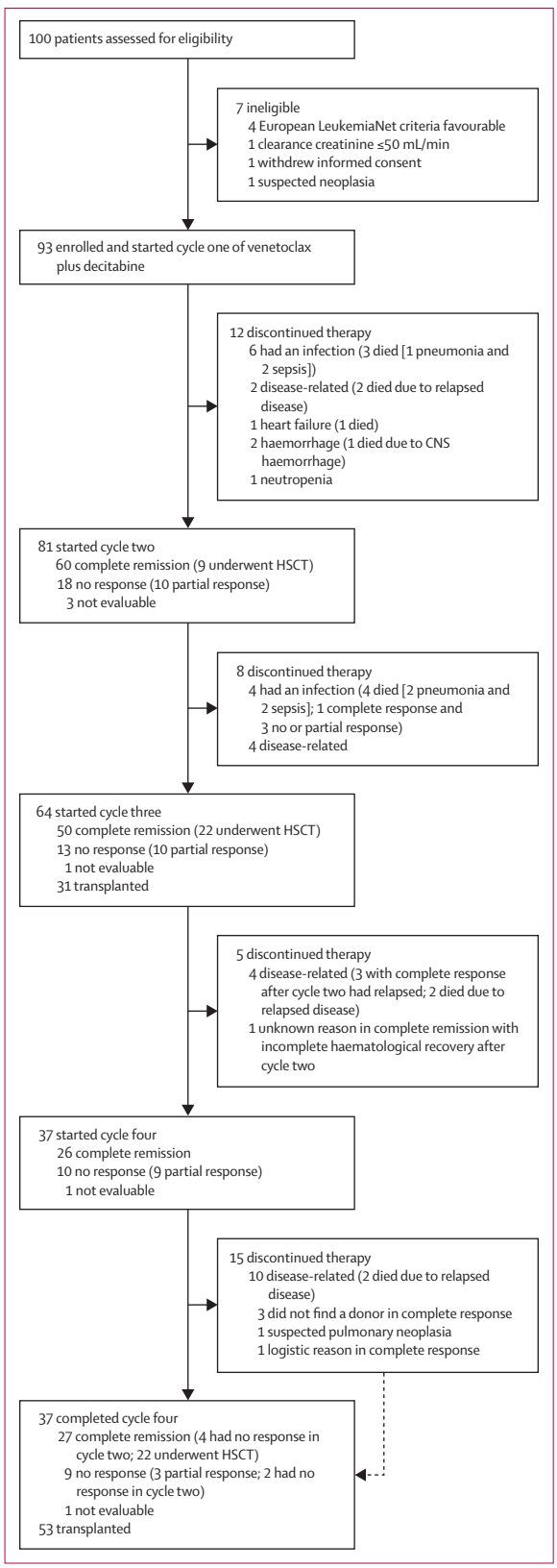

Figure 1: **Trial profile**
The number of patients decreases between cycles as some underwent HSCT and discontinued therapy. HSCT=haematopoietic stem-cell transplantation.

Standard descriptive analyses were used for summarising patient characteristics and treatment outcomes. Continuous variables were analysed using the Mann–Whitney or Wilcoxon test, and categorical variables were analysed using χ^2 or Fisher test. Overall survival, disease-free survival, and GVHD relapse-free survival were evaluated with Kaplan–Meier survival curves. A Fine-Gray regression model for competing risks was used for cumulative incidence of the events of interest, which were acute and chronic GVHD, non-relapse mortality, and cumulative incidence of relapse. Death without the event of interest was considered as a competing event, according to European Bone Marrow Transplantation 2013 guidelines.

To evaluate the correlation between clinical and haematological variables, Pearson correlation index was calculated with the corresponding p value. Correlations with an index value of –0·3 or less and 0·3 or more (and $p<0·05$) were indicative of a not negligible correlation.[16]

An artificial intelligence (AI) framework based on SOPHIA DDM software (version 4.6.0) was used to read and interpret variants detected in the sequenced samples (appendix pp 1–2).[17] The statistical analysis was conducted on R (version 4.3.1; RStudio 2023.09.0 Build 463) and GraphPad PRISM (version 10.1.1).[18,19]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 1, 2021, and Dec 30, 2022, 100 patients were assessed for eligibility (figure 1). Seven (7%) patients were ineligible, which is lower than the expected 12% (appendix p 1). 93 patients started venetoclax plus decitabine induction and were evaluable (44 [47%] at intermediate risk and 49 [53%] at high risk). Table 1 shows baseline clinical, haematological, and genetic characteristics of patients. The median age was 68·5 (IQR 60·3–74·7). All 93 participants were White, of whom 43 (46%) were female and 50 (54%) were male. Comorbidities are shown in the appendix (p 6). Centralised NGS analysis was done at enrolment for 69 (74%) patients. 27 mutated genes were recorded and the most frequently occurring were *DNMT3A* (29 [42%] of 69), *TET2* (20 [29%]), *ASXL1* (19 [28%]), and *CEBPA* (19 [28%]; appendix p 7). The molecular landscape of this cohort is reported in the appendix (pp 7–9), together with the functional clustering of gene mutations and their frequencies. The clustering rationale stemmed from the Cancer Genome Atlas Research Network, which identified six distinct subnetworks within a genome-wide protein–protein interaction network (appendix p 9).

The median follow-up was 236 days (IQR 121–506). 93 patients started cycle one of venetoclax plus decitabine after a median of 17 days (11–27) since enrolment (figure 1). Six patients had to be pretreated with hydroxyurea to reduce leukocytosis (to a target of $<25 \times 10^9$ cells/L). All patients were admitted to hospital before day 1 of cycle one. 74 (80%) patients continued to receive cycle one during hospital stay, whereas the remaining 19 (20%) patients received the rest of cycle one on an outpatient basis. 12 (13%) patients discontinued therapy prematurely between cycle one and two.

81 patients proceeded to cycle two after a median time of 35 days (IQR 29–39) since initiation of cycle one with 63 (78%) treated in an outpatient setting. After cycle two, 60 (74%) of 81 reached complete remission and nine (11%) of those underwent allogeneic HSCT within 2 months, whereas eight (10%) were withdrawn from the study (four due to disease recurrence and four due to lethal infections [two had pneumonia and two had sepsis]). The remaining 51 patients in complete remission who did not undergo transplantation after cycle two faced delays due to searching for suitable donors or logistic challenges. After a median time of 37 days (28–42) since the start of cycle two, 64 patients had initiated cycle three and 56 (88%) were treated in an outpatient setting. After cycle three, 22 (34%) additional responsive patients successfully underwent allogeneic HSCT, and five (8%) discontinued therapy (four due to disease-related causes and one for an unknown reason). Of the three with complete response after cycle two who had relapsed, two died due to relapsed disease.

Subsequently, 37 patients received cycle four (32 [86%] in an outpatient setting) after a median of 36 days (IQR 28–42) since the start of cycle three. After cycle four, 22 (59%) patients underwent transplantation, and 15 (41%) discontinued therapy (ten disease-related causes [two died of relapsed disease], three did not find a donor [all in complete remission], one had suspected pulmonary neoplasia, and one due to logistic reasons [in complete remission]; figure 1). Nine patients in complete remission did not receive allogeneic HSCT (one died due to sepsis, three relapsed, three did not find a suitable donor, one for logistic reasons, and one for unknown reasons).

In total, 64 (69%) of 93 patients reached complete remission and 53 (57%) underwent allogeneic HSCT in complete remission, complete remission with incomplete haematological recovery, or morphological leukaemia-free state in the intention-to-treat population (figure 2). 53 (83%) of 64 patients with complete remission underwent allogenic HSCT. Five (8%) patients in complete remission relapsed before transplantation and four died as a consequence.

MRD evaluation at complete remission and before transplantation is reported in the appendix (p 10). At complete remission after cycles two to four, cytogenetic MRD negativity was observed in ten (24%) of 41 patients, molecular MRD negativity by RT-qPCR in 16 (28%) of 58, and immunophenotypic MRD negativity by flow cytometry in 37 (63%) of 59. At complete remission before allogeneic HSCT, cytogenetic MRD negativity was seen in 18 (44%) patients, molecular MRD negativity in 19 (33%), and immunophenotypic MRD negativity in 38 (64%).

By univariate analysis, no significant correlation was found between cytogenetic, molecular, and mutational alterations and the response to venetoclax plus decitabine treatment assessed after cycle two, except for the *CSF3R* mutation (appendix p 11). The complex karyotype was significantly associated with *TP53* gene mutation (11 patients with a *TP53* mutation had a complex karyotype and two had a normal karyotype, $p<0 \cdot 0001$). A cutoff value of two or fewer altered functions contemporary with five or fewer mutated genes or gene alterations were positively associated with cycle two response ($p=0 \cdot 023$; appendix p 12).

	Patients enrolled (n=93)
Age, years	68·5 (60·3–74·7)
Sex	
Male	50 (54%)
Female	43 (46%)
Race	
White	93 (100%)
Eastern Cooperative Oncology Group score	
0	54 (58%)
1	32 (34%)
2	7 (8%)
Hematopoietic Stem Cell Transplantation Specific-Comorbidity Index	
Low (0)	43 (46%)
Intermediate (1–2)	33 (35%)
High (≥3)	17 (18%)
Italian Lymphoma Foundation score	
Unfit	23 (25%)
Fit	70 (75%)
Patients with comorbidities	50 (54%)
Haemoglobin count, g/dL	8·7 (8·2–9·7)
White blood cell count, $\times 10^6$/L	3·4 (1·8–23·9)
Platelet count, $\times 10^9$/L	53·0 (28·0–115·0)
Bone marrow blasts	40·0% (25·0–70·0)
Circulating blasts	8·0% (2·0–31·0)
Karyotype	
Normal	48 (52%)
Abnormal	41 (44%)
Complex	18 (19%)
Unavailable	4 (4%)
Molecular biology (RT-qPCR, nested-PCR, or HPLC)	
NPM1A	10 (11%)
FLT3-ITD	19 (20%)
FLT3-TKD (n=84)	1 (1%)
WT1 (n=64)	28 (44%)

Data are n (%) or median (IQR).

Table 1: **Baseline characteristics of patients**

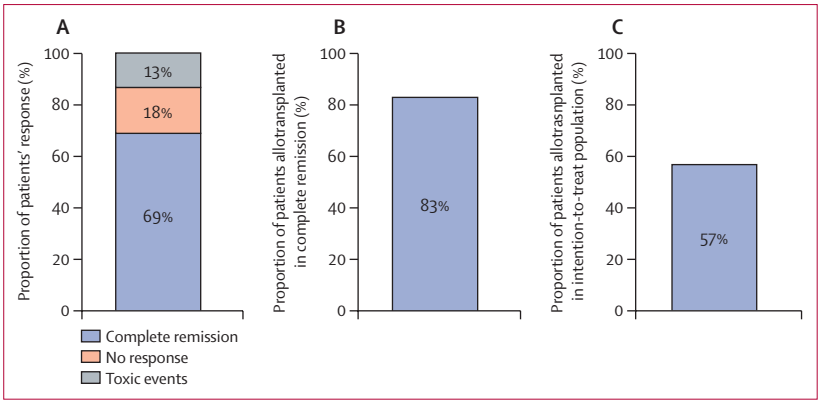

Figure 2: **Disease evaluation and transplantation rate**
(A) 64 (69%) of 93 patients reached complete remission. (B) 53 (83%) of 64 patients with complete remission underwent allogeneic HSCT at the time of analysis. (C) 53 (57%) of 93 patients who received treatment underwent allogeneic HSCT. HSCT=haematopoietic stem-cell transplantation.

	Grade 1–2	Grade 3	Grade 4	Grade 5
Number of adverse events	20	53	42	9
Neutropenia	0	4 (7%)	28 (67%)	0
Thrombocytopenia	0	1 (2%)	1 (2%)	1 (11%)*
Anaemia	0	8 (15%)	4 (10%)	0
Febrile neutropenia	0	13 (24%)†	8 (19%)†	0
Infection	0	31 (58%)	8 (19%)	7 (78%)‡
Atrial fibrillation	0	1 (2%)	0	0
Left ventricular systolic dysfunction	0	1 (2%)	0	0
Heart failure	0	0	0	1 (11%)
Myopericarditis	0	1 (2%)	0	0
Aminotransferases increased	0	1 (2%)	0	0
Hyperuricaemia	0	1 (2%)	0	0
Creatinine increase	0	1 (2%)	0	0
Intestinal obstruction	0	1 (2%)	0	0
Suspected neoplasia	0	0	1 (2%)	0
Mucositis	0	1 (2%)	0	0
Enterocolitis necrotising	0	1 (2%)	0	0
Fever of unknown origin	20 (100%)	0	0	0

Data are n (%). Grade 1–2 events occurring in 10% of patients or more and all grade 3–5 events. *The cause of death was a CNS haemorrhage (n=1). †Febrile neutropenia events were also included in infection events. ‡The causes of death were pneumonia (n=3) and sepsis (n=4).

Table 2: **Adverse events**

Time and dose administration of venetoclax plus decitabine from cycle one to four are reported in the appendix (p 13). In particular, 51 (55%) of 93 patients during cycle one and 36 (44%) of 81 during cycle two received less than 50% of the cumulative venetoclax dose to mitigate the haematological toxic effects. 36 (57%) of 64 patients received less than 75% of the expected dose of venetoclax during cycle three and 24 (64%) of 37 during cycle four. Decitabine was given at the expected scheduled dose in more than 90% of patients in all cycles (88 [95%] of 93 in cycle one, 75 [93%] of 81 in cycle two, 63 [98%] of 64 in cycle three, and 35 [95%] of 37 in cycle four). The causes leading to venetoclax plus decitabine cycling delay are reported in the appendix (p 14).

No cases of tumour lysis syndrome were reported. Adverse events (grade ≥3) occurred in 49 (53%) of 93 patients and resulted in 104 (53%) of all 196 registered adverse events (any grade; table 2). 28 (57%) of 49 patients had infections, including pneumonia, bacterial sepsis, and SARS-CoV-2, that caused seven deaths and three discontinuations from the study. In 17 (35%) patients, neutropenia (grade ≥3) was concurrent with venetoclax plus decitabine treatment (even if present at time of enrolment) but remained quite stable during treatment, except in one who was withdrawn from the study (appendix p 15). The rate of infections slightly decreased throughout the course of study treatment, probably as a consequence of reaching disease response. Thrombocytopenia (grade ≥3) occurred in two (4%) patients, resulting in one fatal CNS bleeding and one acute digestive haemorrhage (table 2). Cardiac events (grade ≥3) occurred in four (8%) patients (left ventricular systolic disfunction, fatal heart failure, atrial fibrillation, and myopericarditis). Nine (10%) patients died (seven due to infections, one had heart failure, and one had a CNS haemorrhage). No treatment-related deaths were observed. The only grade 1–2 adverse event that occurred in 10% of patients or more was fever of unknown origin, irrespective of neutropenia (20 events in 13 [14%] patients).

There was no difference in the fitness of patients at baseline compared with before transplantation (appendix p 16). ECOG performance status, Hematopoietic Cell Transplantation Specific-Comorbidity Index, and Lymphoma Italian Foundation frailty score measured at enrolment and before transplantation remained stable in more than 80% of patients (appendix p 16).

53 patients received allogeneic HSCT (appendix p 17). Median follow-up from the date of transplantation was 1·25 years (IQR 0·73–1·67). The cumulative incidence of non-relapse mortality was 13% (95% CI 6–24) at 100 days, 29% (17–41) at 1 year, and 31% (19–44) at 2 years (appendix p 18), and the causes of death are reported in the appendix (p 19). Eight (15%) patients relapsed after transplantation with cumulative incidence of relapse of 13% (6–24) at 1 year and 16% (7–27) at 2 years (appendix pp 18–19). Non-relapse mortality was statistically associated with *JAK2* (four [67%] of six *JAK2*-positive patients *vs* six [18%] of 33 *JAK2*-negative patients died from non-relapse causes; p=0·028) and *PTPN11* was statistically associated with cumulative incidence of relapse (three [60%] of five *PTPN11*-positive patients relapsed *vs* three [9%] of 35 *PTPN11*-negative patients; p=0·018).

At 1-year, cumulative incidence of any grade acute GVHD was 25% (95% CI 16–39) and grade 2–4 acute GVHD was 11% (5–21; appendix p 18). At 2 years, cumulative incidence of any grade chronic GVHD was 10% (4–21) and moderate-to-severe chronic GVHD was 6% (2–15). Grade and severity of acute and chronic GVHD are reported in appendix (p 19). The overall

survival was 66% (51–77) at 1 year and 57% (41–70) at 2 years, disease-free survival was 60% (45–72) at 1 year and 51% (35–64) at 2 years, and GVHD relapse-free survival was 56% (42–68) at 1 year and 50% (35–64) at 2 years (appendix p 18).

Discussion

Allogeneic HSCT is the only curative option for patients with acute myeloid leukaemia,[2] which justifies the attempts to design new induction treatment programmes as a bridge to allogeneic HSCT for those at high or intermediate risk.

Our study presents a new scenario in the treatment strategy for older patients with acute myeloid leukaemia who are eligible for transplantation. Venetoclax plus decitabine induction/consolidation not only has shown to induce a high rate of complete remission (60 [74%] of 81 at cycle two and 64 [69%] of 93), but also has shown to preserve the patients' clinical fitness, since 53 (57%) patients who received treatment and 53 (83%) of 64 with a complete remission underwent allogeneic HSCT. These data outperform previous reports, in which the percentage of older transplanted patients with acute myeloid leukaemia was around 15–18%.[4,20] Only one study, published in 2023, has indicated that this rate might reach 40% in patients who received decitabine.[6]

Notably, most complete remissions were attained after the second cycle and four unresponsive patients at cycle two reached complete remission after two additional courses of venetoclax plus decitabine, which emphasises the fast anti-acute myeloid leukaemia effect of this regimen. This finding also suggests that continuing the treatment after cycle two in refractory patients can be useful to control disease progression but cannot significantly improve the complete remission rate.

Another noteworthy observation highlights the low rate of disease recurrence during the waiting period for transplantation, even within a high-risk population. Nine (11%) of 60 patients in complete remission after cycle two had allogeneic HSCT within 2 months. The remaining patients underwent one or two additional courses of venetoclax plus decitabine while in complete remission, attributed to logistic or donor search-related delays. Importantly, five (8%) of 64 patients who reached complete remission relapsed and four died. This finding provides physicians with the confidence to thoughtfully plan the transplantation procedure and underlines the need to undergo transplantation as soon as possible, without exceeding 3 months.

Life-threatening infections were the most frequently reported adverse events, especially during the first two cycles of treatment. Subsequently, the incidence of infections decreased in tandem with reaching complete remission. Haemorrhagic events were rare, with one fatal CNS bleeding during the induction phase. All our data support the good safety of venetoclax plus decitabine combination and the need for strict patient monitoring during the early phase with proactive anti-infective control and transfusion support.[21,22]

Mortality did not directly correlate with disease progression and was observed in nine (10%) patients (seven due to infections, one heart failure, and one CNS haemorrhage). Venetoclax dose adjustments were extensively used to mitigate the prolongation of cytopenia and risk of complications in this high-risk population of older patients with acute myeloid leukaemia.[23] Notably, 51 (55%) of 93 patients during cycle one and 36 (44%) of 81 during cycle two received less than 50% of the cumulative venetoclax dose, 36 (57%) of 64 received less than 75% of the expected dose of venetoclax during cycle three, and 24 (64%) of 37 during cycle four, whereas more than 90% of patients received decitabine at the expected scheduled dose. As a result, most patients were able to continue treatment in an outpatient setting with a low number of adverse events leading to treatment discontinuation, underscoring the feasibility and safety of this regimen, especially after reaching complete remission.[23] Additionally, the possibility to deliver acute myeloid leukaemia therapy in an outpatient setting offers the opportunity to substantially reduce the costs associated with extended hospital stay for intensive chemotherapy.[24]

Another important observation pertains to the sustained preservation of patients' physical fitness during treatment. The assessment of ECOG performance status, Hematopoietic Cell Transplantation Specific-Comorbidity Index, and Lymphoma Italian Foundation frailty score at enrolment and before transplantation showed that more than 80% of the enrolled patients were fit for transplantation at enrolment and almost all maintained a stable clinical fitness until allogeneic HSCT. None of the patients in complete remission were prevented from undergoing transplantation because of degradation of fitness. This stability in fitness allowed transplantation and could possibly influence outcomes of the transplantation procedure.[25–27] In this regard, venetoclax plus decitabine treatment appears to favourably influence transplantation outcomes. No graft failures were observed, and the incidence of non-relapse mortality, relapse mortality, and acute and chronic GVHD was very low.

Considering the single-arm design of this trial, we were not able to directly compare the results to a chemotherapeutic-based approach, which should be acknowledged. At this time, no significant correlation between the rate of complete remission and biological characteristics was identified, highlighting the need for continued research to elucidate factors influencing treatment response. Our data suggests that a cutoff value of two or fewer altered functions contemporary with five or fewer mutated genes or genes' alterations could be favourably associated with response to therapy at cycle two. However, due to the small number of patients, further investigation is warranted to delineate the implications of these findings.[28–30]

In conclusion, this study shows that a pretransplantation venetoclax plus decitabine can significantly enhance the feasibility of allogeneic HSCT in older patients with acute myeloid leukaemia who are deemed fit for transplantation at the time of diagnosis.

Contributors

DR conceptualised the study, wrote the protocol, did the data curation, formal analysis, wrote the original manuscript, and was responsible for project administration. NP wrote the protocol, did the data curation, formal analysis, and wrote the original manuscript. SiB wrote the protocol, collected the data, conducted next-generation sequencing (NGS) analysis, and wrote the original manuscript. DR, NP, SS, MF EB, FO, LC, StB, AMC, RS, MaM, CA, AO, GB, AC, CV, SL, VM, ET, MB, PG, PM, RC, LuiG, CS, and VR conducted the study . MF collected the data, did the formal analysis, and wrote the original manuscript. MaM wrote the protocol as the Gruppo Italiano per il Trapianto di Midollo Osseo (GITMO) trial officer. MV did the formal analysis and was responsible for RedCap database management. SC conceptualised the study, did the formal analysis, and was responsible for RedCap database management. AL and LucG did the data collection, formal analysis, and NGS analysis. CB did the NGS analysis. SP did the formal analysis. MiM wrote the protocol and the original manuscript. FC wrote the protocol as the GITMO president and wrote the original manuscript. All the authors critically reviewed and approved the final manuscript. DR, NP, SiB, MF, AL, LucG, and MiM accessed and verified all the data in the study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

DR received consulting fees from Medac; honoraria and travel grants from Jazz Pharma, Novartis, MSD, Kite Gilead, and Medac; and has participated in data safety monitoring and advisory board meetings for Novartis, MSD, Kite Gilead, Medac, AbbVie, and Janssen. EB received consulting fees from AbbVie; travel grants from Amgen, Novartis, and AbbVie; and has participated in data safety monitoring and advisory board meetings for Otsuka and Amgen. FO received honoraria from Takeda, Medac, and Kyowa; and travel grants from Roche, Janssen, Kyowa, Takeda, Jazz Pharma, and Medac. RS received a travel grant from Takeda. MaM received honoraria from Novartis, MSD, Astellas Pharma, AbbVie, Takeda, Pfizer, Sanofi, Jazz Pharma, Janssen Cilag, Kite Gilead, Medac, and Bristol Myers Squibb; travel grants from Kite Gilead, Roche, and Janssen Cilag; has participated in data safety monitoring and advisory board meetings for Novartis, Takeda, Kite Gilead, Pfizer, Bristol Myers Squibb, and Janssen Cilag; and served as president of GITMO. CA received honoraria from AbbVie and Jazz Pharma; and has participated in data safety monitoring and advisory board meetings for AbbVie, Jazz Pharma, and Amgen. GB received travel grants from Janssen Cilag and Amgen. AC received honoraria from AbbVie, Menarini (Stemline), Pfizer, Jazz Pharma, and Servier; a travel grant from Jazz Pharma; and has participated in data safety monitoring and advisory board meetings for AbbVie and Menarini (Stemline). CG received consulting fees from AbbVie, Jazz Pharma, Incyte, Bristol Myers Squibb, and Astellas; and a travel grant from Jazz Pharma. PM received honoraria and travel grants from AbbVie and Johnson & Johnson. LG received honoraria from Novartis, MSD, Gilead, AbbVie, Sanofi, and Bristol Myers Squibb; and travel grants from Janssen and AbbVie. CS received honoraria from Jazz Pharma and Kite Pharma; and a travel grant from Jazz Pharma. VR received travel grants from Neovii, Medac, and Jazz Pharma. All other authors declare no competing interests.

Data sharing

Clinical results and molecular data from published parts of this trial can be made available upon request to the Corresponding author and decision of the principal investigator (domenico.russo@unibs.it).

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