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Review Article

Venetoclax and Azacitidine Combination Therapy in Unfit Patients with Newly Diagnosed Acute Myeloid Leukemia

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Summary

Adding venetoclax to azacitidine produced the first meaningful survival gain for patients unfit for intensive chemotherapy, and the regimen became standard within two years. Practice has since diverged from the trial protocol, and the modifications appear to work.

Objectives: To review the published evidence on venetoclax combined with azacitidine in newly diagnosed acute myeloid leukaemia in patients unfit for intensive therapy: what the pivotal trial demonstrated, what the toxicity costs, how outcomes compare in routine care, and what the modifications adopted in practice have achieved.

Material and Methods: Narrative review of randomised trials, prospective real-world cohorts, retrospective series and consensus recommendations indexed in PubMed and the major haematology journals. Studies were eligible if they reported efficacy, toxicity or outcome of venetoclax-based combination therapy in a defined newly diagnosed acute myeloid leukaemia population unfit for intensive chemotherapy. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: In the pivotal randomised trial, median overall survival was 14.7 months with the combination against 9.6 months with azacitidine alone (HR 0.66, 95% CI 0.52-0.85, $p < 0.001$), composite complete remission 66.4 against 28.3 per cent and complete remission 36.7 against 17.9 per cent. Grade 3 or higher febrile neutropenia occurred in 42 against 19 per cent, neutropenia in 42 against 29 and thrombocytopenia in 45 against 38 per cent. In a prospective real-world cohort, median survival was 13.0 months (95% CI 11.4-15.7) and matched comparison against the trial population gave 14.8 against 14.9 months ($p = 0.6$), with 30-day mortality of 2.6 per cent against 7 per cent in the trial. Survival differed by genetic risk group at 24.5, 15.4 and 8.9 months. Shortening venetoclax from 28 days produced comparable remission rates with less febrile neutropenia in several series.

Conclusion: The survival benefit is established and the regimen is appropriately standard. Its dominant toxicity is myelosuppression, and routine practice has converged on shortening venetoclax exposure faster than trials have tested it, with early outcomes suggesting the modification is sound.

Abbreviations: AML – Acute Myeloid Leukaemia, ND – Newly Diagnosed, VEN – Venetoclax, AZA – Azacitidine, HMA – Hypomethylating Agent, LDAC – Low-Dose Cytarabine, CR – Complete Remission, CRi – Complete Remission with Incomplete Haematological Recovery, CRc – Composite Complete Remission, OS – Overall Survival, ELN – European LeukemiaNet, G-CSF – Granulocyte Colony-Stimulating Factor, HR – Hazard Ratio.

Keywords: *Acute Myeloid Leukaemia; Venetoclax; Azacitidine; Unfit Patients; Febrile Neutropenia*

Introduction

Acute myeloid leukaemia has a median age at diagnosis near 68 years, and close to half of patients are judged unsuitable for intensive induction chemotherapy on grounds of age, comorbidity or performance status [1,2,3]. For decades that group had no treatment that improved survival materially, and hypomethylating agents given alone produced median survival around ten months [4,5].

Venetoclax is a selective inhibitor of BCL-2, an anti-apoptotic protein on which leukaemic blasts depend more heavily than normal haematopoietic cells [6]. Early phase work combining it with a hypomethylating agent in patients over 65 produced composite remission rates

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and survival that exceeded anything previously reported in this population, prompting regulatory approval before the confirmatory trial reported [7,8].

That trial then confirmed the benefit and the combination became standard of care within two years [9,10]. This review sets out what it demonstrated, what it costs in toxicity, whether the result holds in routine practice, and what the modifications that practice has adopted have achieved.

Material and Methods

Search strategy: PubMed and the archives of the major haematology journals were searched for studies of venetoclax-based combination therapy in acute myeloid leukaemia. Search terms combined venetoclax with azacitidine, hypomethylating agent, unfit, ineligible for intensive chemotherapy, VIALE-A, real-world and dose modification. Reference lists of retrieved trials and cohorts were screened by hand.

Eligibility: Studies were included if they reported efficacy, toxicity or survival outcomes for venetoclax combined with a hypomethylating agent or low-dose cytarabine in newly diagnosed patients unfit for intensive chemotherapy. Studies in relapsed or refractory disease are cited where they inform interpretation and are identified as such.

Data extraction and handling: Design, cohort size, median age, venetoclax schedule, concomitant azole use and reported outcomes were extracted as published. Venetoclax duration and dose adjustment for azole co-administration are stated alongside every outcome figure, because these are the variables on which routine practice most often departs from the trial protocol. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What the trial showed: The pivotal study randomised 431 previously untreated patients ineligible for intensive chemotherapy in a two-to-one ratio to azacitidine at 75 mg/m² for seven days every 28 days with either venetoclax at 400 mg daily continuously or placebo [9]. At a median follow-up of 20.5 months, median overall survival was 14.7 months against 9.6 months, with a hazard ratio for death of 0.66 (95% CI 0.52 to 0.85, $p < 0.001$) [9].

Response was substantially deeper. Composite complete remission was achieved in 66.4 against 28.3 per cent and complete remission in 36.7 against 17.9 per cent, both $p < 0.001$ (Figure 1) [9,10]. Response also came faster: median time to composite remission was one month and 40 per cent of patients reached it before cycle 2, against 5.5 per cent in the control arm [10]. Estimated survival at 24 months was 37.5 against 16.9 per cent [11].

The comparator was appropriate rather than a straw man. Median survival of 9.6 months with azacitidine alone is consistent with the roughly ten months reported in the trial conventionally used as the historical benchmark for this population [4,10].

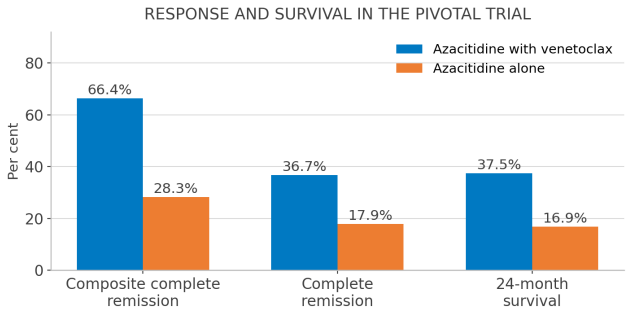

Figure 1: Response and survival in the randomised trial of 431 patients [9,10,11]

What it costs: The toxicity is haematological and substantial. Grade 3 or higher febrile neutropenia occurred in 42 per cent of patients receiving the combination against 19 per cent on azacitidine alone, neutropenia in 42 against 29 per cent and thrombocytopenia in 45 against 38 per cent (Figure 2) [9]. Nausea of any grade affected 44 against 35 per cent [9].

Serious events reported separately included febrile neutropenia in 30 against 10 per cent and pneumonia in 16 against 22 per cent, the latter favouring the combination [10]. Laboratory tumour lysis syndrome was rare, occurring in three patients, and 30-day mortality was 7 per cent against 6 per cent, essentially unchanged [10]. Patients received a median of seven cycles of the combination against 4.5 of azacitidine alone [10].

The pattern is that the combination does not increase early death but does produce prolonged cytopenias requiring dose interruption, transfusion and hospital admission for neutropenic fever [9,10]. That is the toxicity profile that has driven the modifications discussed below.

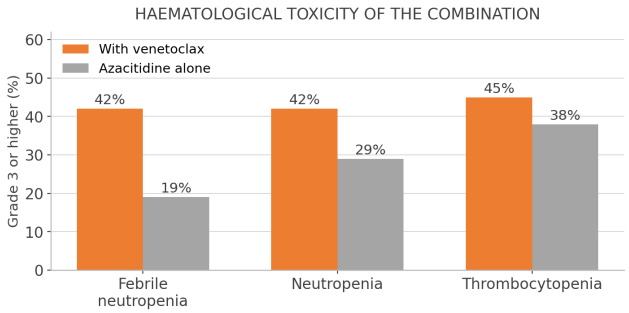

Figure 2: Grade 3 or higher haematological toxicity in the randomised trial [9]

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Study	n	Design	Principal reported finding
DiNardo et al. 2019 [7]	145	Phase Ib/II	Composite remission 66%; median survival 17.5 months
DiNardo et al. 2020 [9]	431	Randomised	Median survival 14.7 against 9.6 months
Wei et al. 2020 [12]	211	Randomised	Venetoclax with low-dose cytarabine evaluated
Czech cohort [13]	163	Real-world	Seven hospitals; median age 72
Palmieri et al. 2026 [14]	Prospectiv e	Real-world	Median survival 13.0 months; matched to trial
Hokkaido series [15]	—	Retrospecti ve	14, 21 and 28-day schedules comparable

Table 1: Principal studies reviewed, with design and the finding as reported by the original investigators

Whether it holds outside a trial: A prospective real-world study reported median overall survival of 13.0 months (95% CI 11.4 to 15.7) with one-year and two-year survival of 52.4 and 29.6 per cent [14]. Composite complete remission reached 73 per cent by the end of cycle 4, with 54 per cent responding before cycle 2, and achieving remission within four cycles was associated with significantly longer survival at 19.1 months [14].

Matched comparison against the trial population gave median survival of 14.8 against 14.9 months (p = 0.6), which is unusually close agreement between routine care and a registration trial [14]. Early mortality in routine practice was 2.6 per cent at 30 days and 6.7 per cent at 60 days, against 7 per cent at 30 days in the trial (Figure 3) [10,14].

A real-world mortality figure lower than the trial's is worth pausing over. It probably reflects accumulated familiarity with managing the cytopenias, alongside patient selection by clinicians who can decline to treat someone a protocol would have enrolled [13,14]. It does not suggest the trial overstated toxicity.

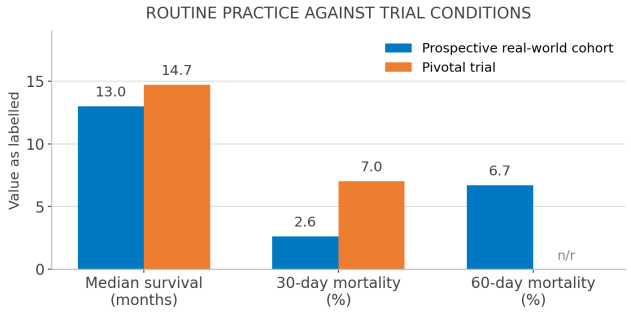

Figure 3: Prospective real-world outcomes against the randomised trial [9,10,14]

Genetic risk still separates outcome: The combination does not abolish the prognostic effect of disease genetics. In the real-world cohort, median survival by 2017 risk category was 24.5 months for favourable, 15.4 for intermediate and 8.9 for adverse-risk disease (Figure 4) [14]. The spread is wide enough that the average figure of 13 to 15 months describes no particular patient well.

That has a practical consequence for consent. A patient with favourable-risk disease and one with adverse-risk disease are being offered the same regimen with expected survival differing by more than a year, and current risk classification identifies which is which at diagnosis [16,17].

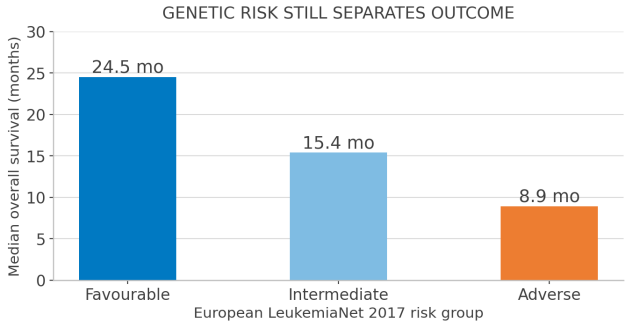

Figure 4: Median survival by genetic risk group in routine practice [14]

How practice has modified the regimen: The protocol specifies venetoclax continuously for 28 days of each cycle, and routine practice frequently does not follow it. Shorter courses of 14 or 21 days, dose reduction for concomitant azole antifungals, and granulocyte colony-stimulating factor support have all been adopted to limit myelosuppression [13,15,18].

Comparison of 14, 21 and standard 28-day venetoclax in the first cycle found comparable outcomes across the three schedules [15]. A smaller series comparing 14 against 28 days reported composite remission of 75 against 80 per cent with febrile neutropenia in 37.5 against 80 per cent and shorter hospital stay, though with 13 patients the numbers permit no firm conclusion [18]. A systematic review has examined the parallel question of venetoclax with low-dose cytarabine, which was never compared directly against the azacitidine combination [12,19].

Modification	Rationale	Evidence
14 or 21-day venetoclax	Reduce myelos uppression	Comparable remission in retrospective series [15,18]
Dose reduction with azoles	Pharmacokineti c interaction	Widely practised; outcomes not formally compared [13]
Growth factor support	Shorten neutropenia	Used in routine care; not in the trial protocol [13]
Low-dose cytarabine instead	Alternative partner	Never compared head to head with azacitidine [12,19]

Table 2: Modifications adopted in routine practice and the evidence behind each

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Where the combination sits among the alternatives: For fitter older patients with high-risk or secondary disease, a liposomal formulation of daunorubicin and cytarabine extends median survival against conventional induction [22], and for those reaching remission after chemotherapy, oral azacitidine maintenance prolongs survival further [23]. The venetoclax-based combination occupies the space between intensive therapy and supportive care, and its boundaries with both are defined by fitness assessment rather than by comparative trials [10,24].

That matters because fitness is judged clinically. A patient assessed as unfit and given the combination, and one assessed as fit and given intensive therapy, have never been compared in a randomised design at the boundary between the two categories [9,22]. Guidance sets out the considerations without resolving the question [10,24].

Response assessment has also not settled. Measurable residual disease carries prognostic weight in acute myeloid leukaemia generally [25], and residual disease-negative remission on venetoclax-based therapy is associated with better outcome, but whether it should trigger a change of treatment in a population defined by unfitness for anything more intensive is unresolved [10,25].

Population	Standard approach	Evidence
Fit, standard risk	Intensive induction	Long-established; not compared with venetoclax combination [10,24]
Fit, high-risk or secondary	Liposomal daunoru bicin-cytarabine	Randomised superiority over conventional induction [22]
Unfit for intensive therapy	Azacitidine with venetoclax	Randomised superiority over azacitidine alone [9]
In remission after chemotherapy	Oral azacitidine maintenance	Randomised survival benefit [23]

Table 3: Where the combination sits among treatment options, and the evidence defining each

Reviews and guidance: The combination has been discussed as a paradigm shift in how this population is treated [8], and summaries of current progress place it alongside the targeted agents developed over the same period [20,21]. What distinguishes it is breadth: unlike FLT3, IDH1 or IDH2 inhibitors, it applies to unfit patients regardless of molecular subtype [20,21].

Discussion

The efficacy question is settled. A hazard ratio of 0.66 for death, composite remission more than doubled and survival extended from 9.6 to 14.7 months represent the largest advance this population has seen [9,10]. Matched real-world comparison reproducing the trial figure almost exactly is unusual and strengthens the case considerably [14].

The interesting question is what happens next, and it concerns the regimen rather than the drugs. Febrile neutropenia in 42 per cent of patients is the dominant toxicity, and clinicians have responded by shortening venetoclax exposure without waiting for trial evidence [9,13,15,18]. That is a rational response to a toxicity concentrated in a frail population, and the early data suggest it does not cost response.

Practice moving ahead of evidence

Shortened venetoclax schedules are now common enough that several series report them as routine [13,15,18], and the comparisons available are retrospective, small, and subject to the obvious confound that patients given shorter courses may have been those tolerating treatment less well. The finding of comparable remission with less febrile neutropenia could therefore be genuine or could reflect selection.

This is a familiar pattern in oncology and not necessarily a problem. Where a modification reduces toxicity and observation suggests efficacy is preserved, adoption ahead of formal testing is defensible in a population for whom the toxicity is the limiting factor. What follows is that a randomised comparison of schedule length would be worth more now than another comparison of partner agent [15,19].

Study limitations

The limitations belong to the underlying literature. The pivotal trial defined unfitness by age of 75 or above or specified comorbidities, and that definition does not map precisely onto how fitness is judged in practice [9]. Real-world cohorts are subject to selection by treating clinicians, which operates in the opposite direction to trial eligibility criteria and may explain the lower early mortality observed [13,14]. Comparisons of venetoclax schedule length are retrospective and small, with one series comprising 13 patients [15,18]. Concomitant azole use alters venetoclax exposure substantially and is inconsistently reported across cohorts [13]. And follow-up in the real-world studies remains shorter than in the trial, so late differences cannot yet be excluded [14].

Two gaps deserve naming. No randomised trial has compared shortened against standard venetoclax duration, despite shortened schedules being widely used [15,18]. And venetoclax with azacitidine has never been compared directly against venetoclax with low-dose cytarabine, so the assumed superiority of the former rests on cross-trial comparison [12,19].

Conclusion

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Venetoclax added to azacitidine extends median survival from 9.6 to 14.7 months in patients unfit for intensive chemotherapy, more than doubles composite complete remission from 28.3 to 66.4 per cent, and produces response within a month in 40 per cent of patients. A prospective real-world cohort matched to the trial population reported 14.8 against 14.9 months, with lower early mortality at 2.6 per cent against 7 per cent. Genetic risk still separates outcome sharply, from 24.5 months in favourable-risk to 8.9 in adverse-risk disease. The limiting toxicity is myelosuppression, with grade 3 or higher febrile neutropenia in 42 per cent, and routine practice has responded by shortening venetoclax exposure to 14 or 21 days with comparable reported remission rates. That modification is now common and has never been tested against the standard schedule in a randomised trial, which is the most useful comparison remaining to be done.

Two further questions follow from the survival figures rather than the toxicity. Median survival of 13 to 15 months describes a group whose members range from 24.5 months to 8.9 depending on genetic risk [14], so the aggregate figure is of limited use in discussing prognosis with an individual patient. Reporting outcomes by risk group as a matter of routine would serve that conversation better than reporting the median alone [14,16,17].

And the boundary with intensive therapy remains defined by clinical judgement rather than evidence. A patient assessed as borderline could reasonably receive either approach, and no trial has randomised at that boundary [9,22]. Given that the combination now achieves composite remission in two thirds of unfit patients, whether some fit patients would do as well on it is a question worth asking rather than assuming the answer to.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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