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MEDICINE FIELD

„ACUTE MYELOBLASTIC LEUKEMIA IN THE ELDERLY. PROGNOSTIC FACTORS AND RESPONSE TO NEW THERAPIES”

SUMMARY OF THE DOCTORAL THESIS

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Introduction – Fundamental Issue and Justification of the Topic

Acute myeloid leukemia (AML) in the elderly represents a complex pathology with a significant impact on survival, due to biological vulnerability, frequent comorbidities, and unequal access to modern therapies. Despite recent advances, the optimal treatment for this category of patients remains a significant challenge in current hematologic practice.

Given these clinical and biological challenges, a detailed evaluation of the characteristics of elderly patients with AML and their response to various therapeutic options becomes essential for optimizing treatment and improving prognosis. This thesis aims to define a specific clinical and biological profile of elderly patients diagnosed with acute myeloid leukemia (AML) and to identify relevant predictive factors for response to current therapies. The primary goal is to establish practical guidelines for personalized treatment, emphasizing the balance between efficacy and tolerability.

To understand the particularities of this disease, it is important to note that acute leukemias represent a heterogeneous group of malignant disorders of hematopoietic stem cells, characterized by the accumulation of immature clones and severe dysfunction of medullary hematopoiesis [1].

The working hypothesis was based on the assumption that specific clinical-biological characteristics and demographic parameters (age, sex) significantly influence therapeutic response and patient prognosis. Based on this hypothesis, the research objectives included both the analysis of these factors and a comparative evaluation of the effects of intensive chemotherapy and treatment with hypomethylating agents, with or without Venetoclax, on survival and quality of life.

The thesis is structured into two parts: a general section that synthesizes recent data from the literature regarding AML in the elderly, and a special section that integrates the results of two retrospective clinical studies. The first study analyzed a group of patients eligible for intensive treatment, while the second included patients treated with non-intensive regimens, primarily hypomethylating agents, based on their functional and biological profiles.

The limitations identified during the research mainly concerned the limited access to cytogenetic and molecular biology testing. This constraint affected the ability to perform a complete and uniform stratification for all patients based on these essential parameters.

Consequently, I emphasize the need to expand and standardize these investigations during initial assessment, in order to ensure rigorous classification and the most appropriate therapeutic approach for each case.

1. Theoretical Aspects Regarding Prognosis and Therapeutic Options in AML in the Elderly

Elderly patients with acute myeloid leukemia (AML) are generally defined as being over 60–65 years of age [2]. The median age at diagnosis is approximately 70 years, highlighting the significant impact of the disease on this population [3]. In practice, advanced age is often considered an exclusion criterion from intensive chemotherapy due to the poor prognosis [2]. This is determined by both the presence of multiple comorbidities and an unfavorable genetic profile, characterized by an increased frequency of TP53, ASXL1, and SRSF2 mutations, and a reduced presence of NPM1 mutations, which are associated with a favorable prognosis [2].

The assessment of biological and clinical frailty using HCT-CI, CCI scores, and ECOG performance status is essential in determining the therapeutic approach [4]. Common comorbidities such as cardiovascular diseases, renal insufficiency, and cognitive impairment reduce treatment adherence and limit therapeutic options [5]. Compared to the general population, elderly AML patients have a significantly increased risk of cardiovascular conditions (4.6 times), type 2 diabetes mellitus (3.8 times), and strokes (2.6 times) [6].

Comprehensive geriatric assessment plays a fundamental role in personalizing therapy, encompassing the analysis of physical, cognitive, nutritional, psycho-emotional, and social functions, as well as social support [5]. This enables the avoidance of overtreatment in frail patients and undertreatment in those who could benefit from more intensive strategies [5]. Tailoring therapy to the individual patient profile improves both clinical outcomes and quality of life [6].

1.1. Conventional Chemotherapy and Low-Intensity Regimens

The choice of therapeutic strategy in elderly AML patients is complex, influenced by both the general condition and frequent comorbidities, as well as the biological features of the disease, including adverse mutations such as TP53, the presence of secondary AML, or therapy-related AML [3,7–10].

Treatment resistance is determined by factors such as genomic instability, unfavorable karyotype, and expression of immature phenotypes [11,12]. Compared to younger patients, the elderly less frequently present favorable cytogenetics and the NPM1 mutation [13]. Standard induction chemotherapy with anthracycline and cytarabine may achieve complete remission rates of up to 60% in patients over 60 years old. However, the associated toxicity limits its use to those with an adequate performance status [11]. Patients eligible for intensive chemotherapy have a median overall survival of approximately 12 months, whereas ineligible patients have shorter median survival times, ranging from 3 to 10 months [11, 14–16].

The decision-making algorithm for treating elderly AML patients is presented in Figure 1.1.

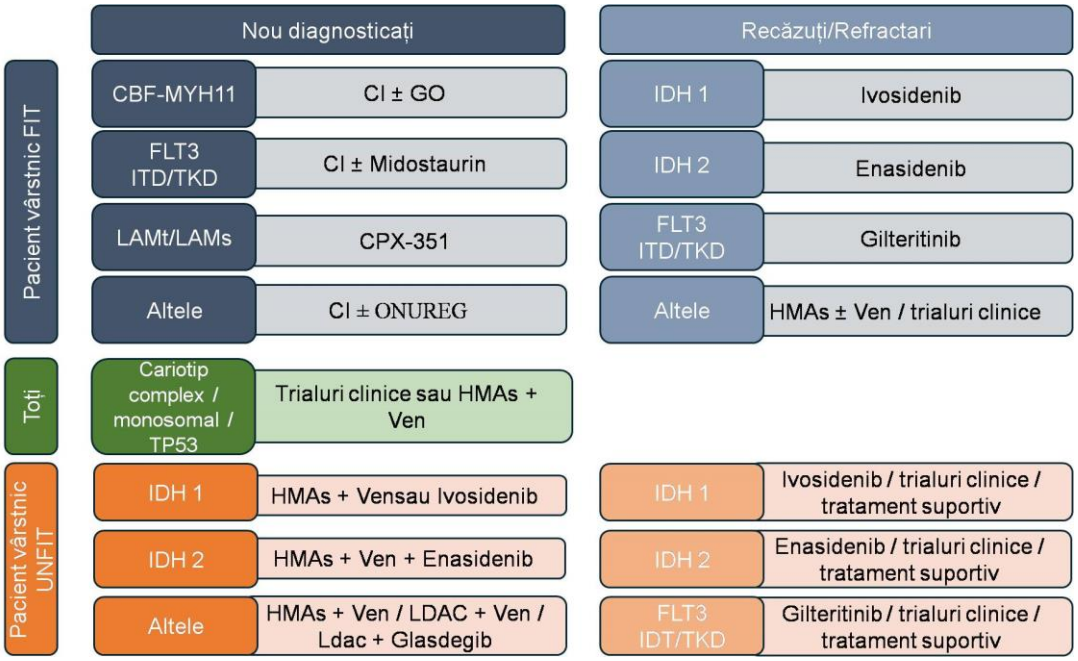

Figure 1.1. Treatment algorithm for elderly patients with AML, adapted with permission from "Older Patients with Acute Myeloid Leukemia Deserve Individualized Treatment" [3].

2. Working Hypothesis and General Objectives

Working Hypothesis

The working hypothesis of this thesis starts from the premise that specific clinical and biological characteristics, as well as demographic parameters, significantly influence the therapeutic response and survival of elderly patients diagnosed with AML. Identifying these factors could contribute to a more rigorous selection of therapeutic strategies.

General Objective of the Thesis

The main objective of this study was to evaluate prognostic factors and therapeutic response in elderly AML patients, treated differently depending on their eligibility for intensive chemotherapy.

Specific Objectives

- To compare clinical and molecular characteristics between the two analyzed cohorts
- To assess the type and duration of therapeutic response, including complete remission and MRD
- To estimate overall survival (OS) and progression-free survival (PFS)
- To identify factors associated with relapse, early death, and transfusion independence
- To analyze the prognostic value of clinical scores and biological parameters

3. General Methodology of the Research

This study was conducted at the Hematology Clinic of Colțea Clinical Hospital through a retrospective analysis of two cohorts of elderly patients diagnosed with acute myeloid leukemia (AML) who were treated between 2017 and 2023. The research was structured into two directions: the first assessed patients eligible for intensive chemotherapy, and the second included cases treated with hypomethylating agents or other innovative therapies, depending on eligibility and biological profile.

Patients aged 65 years or older, diagnosed with de novo or secondary AML, who received complete treatment in the clinic and had available relevant clinical and paraclinical

data, were included. These data included performance status (ECOG), comorbidity scores (CCI and HCT-CI), hematological tests, cardiac evaluation (LVEF), and cytogenetic and molecular investigations. All patients were included after obtaining informed consent, and the ethics committee approved the research protocol.

The data were extracted from medical records and entered into an electronic database. For previously diagnosed cases, data entry was done retrospectively, while for recent cases, information was recorded directly at the time of presentation to the clinic.

The diagnostic evaluation included a complete blood count, peripheral blood smear, biochemistry tests, bone marrow aspirate, flow cytometry, molecular testing, and cytogenetic analysis. These investigations were conducted in accordance with the internal protocol, with support from the National Oncology Program.

To assign prognostic risk groups, the 2017 ELN classification was used, which was in effect at the time of diagnosis for most patients. Risk group stratification was based on available cytogenetic and molecular data. In cases where only one of these investigations was available, classification was performed using the information available at that time.

3.1. Statistical Data Processing

Clinical, biological, and therapeutic data were compiled in an Excel database and statistically analyzed using SPSS software, version 26. The chi-square test was applied to compare frequencies between groups and to assess associations between clinical-biological variables and therapeutic response or survival.

To estimate overall survival (OS) and progression-free survival (PFS), the Kaplan–Meier method was used. Differences between survival curves were compared using the log-rank test (Mantel-Cox), supplemented by the Breslow and Tarone-Ware tests. Median and mean survival values were reported along with 95% confidence intervals.

The impact of clinical-biological factors on the hazard of death or relapse was assessed using Cox regression. Interpretation of results was based on hazard ratios (HR), p-values, and 95% confidence intervals. Cases with $p < 0.05$ were considered statistically significant, while values between 0.05 and 0.10 were interpreted as having a trend toward association.

To identify independent factors associated with achieving therapeutic response or survival beyond six months, a multivariate analysis using binary logistic regression was conducted. The models included variables such as age, ECOG score, CCI score, left

ventricular ejection fraction, and type of treatment administered. Results were expressed as odds ratios (OR), with 95% confidence intervals and corresponding statistical significance.

Therapeutic response was defined according to standard hematologic criteria: complete response (CR – <5% bone marrow blasts and hematologic recovery), incomplete complete response (CRi – <5% blasts without full hematologic recovery), partial response (PR – partial reduction in blast percentage), and lack of response. The significance threshold was set at $p < 0.05$ in all analyses.

4. Summary of the Special Part of the Thesis

4.1. Study 1 – Evaluation of Elderly AML Patients Undergoing Intensive Chemotherapy

Acute myeloid leukemia (AML) in elderly patients represents a major therapeutic challenge due to the frequent association with frailty, multiple comorbidities, and adverse tumor biology. The first direction of the research aimed to evaluate patients treated with intensive chemotherapy (IC), to identify factors correlated with therapeutic response and survival.

The study included 48 patients aged 65 years or older, diagnosed with AML between 2017 and 2023, with the majority (93.8%) between 65 and 74 years old. There was a balanced gender distribution, and the patients predominantly had an urban origin (87.5%). The most common FAB subtypes were M4 (35.4%), M2 (29.2%), and M1 (22.9%), and 87.5% of cases were de novo AML. Hyperleukocytic forms were identified in 56.2% of patients, and bone marrow infiltration (>50% blasts) was present in 68.7% of cases ($p = 0.009$). Leukocytosis was reported in 62.5% of cases ($p < 0.001$), and severe thrombocytopenia (platelet count < 20,000/mm³) in 25% of patients ($p = 0.009$). Hemoglobin <8 g/dL was present in 60.4% of patients ($p = 0.149$), without statistical significance. Functional status was good in most cases (ECOG 0–1 in 97.9%; $p < 0.001$), but high comorbidity scores were frequent: CCI >4 in 81.3% ($p < 0.001$) and HCT-CI ≥3 in 56.2% of patients ($p = 0.002$). The total number of comorbidities was three or more in 62.5% of cases.

The 2017 ELN classification was applied based on the availability of cytogenetic and/or molecular data. Among patients tested cytogenetically (n = 25), 84% were classified as intermediate risk, and 76% had a normal karyotype ($p < 0.001$). In molecular testing (n = 40), 35% of cases showed mutations, most commonly FLT3-ITD and TKD. Molecular risk was classified as intermediate in 90% of cases and favorable in 10%.

The therapeutic response after induction included complete remission (CR) in 43.5% of patients and partial response (PR) in 8.7% of patients. Early mortality was 17.4%, mainly due to infectious or hemorrhagic complications. Almost half of the patients with a favorable response became independent of red blood cell and platelet transfusions, with a robust correlation between the two types of transfusion independence ($\gamma = 0.900$; $p < 0.001$).

Relapse occurred in over half of the initially responsive cases, especially within the first 12 months after treatment. However, stable disease under second-line treatment was also reported, including in patients without complete response, supporting the importance of sustained monitoring after remission. Median overall survival (OS) was 11 months, and progression-free survival (PFS) was 6.2 months.

Multivariate analysis highlighted the negative impact of low functional status and high HCT-CI score on survival. These results underscore the need for a rigorous selection of patients eligible for intensive treatment, considering not only age but also functional reserve and the burden of comorbidities. Achieving remission is possible even in cases with a high biological risk, but maintaining it requires a carefully adapted post-induction strategy, which should include, when feasible, assessment of minimal residual disease (MRD).

Discussion

The decision to administer intensive chemotherapy to elderly AML patients should be based more on functional status and biological profile than on chronological age. Clinical scores, such as ECOG, CCI, and HCT-CI, provide essential information not only for initial selection but also for estimating therapeutic response and predicting survival. Recent studies have shown that elderly patients with ECOG scores of 0–1 can benefit comparably to younger individuals from intensive treatment (Choi et al., 2023). Comprehensive geriatric assessment also contributes to more accurate stratification of toxicity and mortality risk (Min et al., 2022) [17,18].

Sex-based analysis revealed a significant discrepancy: women more frequently responded to treatment (16/28), yet also accounted for the majority of early deaths (6/7).

This paradox may reflect biological or comorbid factors not fully captured by standard scoring systems. The literature supports the use of extended geriatric assessments better to anticipate treatment-related toxicities and resilience [18,19].

Cytogenetic testing was available for over half of the patients, and most exhibited a normal karyotype, being classified in the intermediate-risk group. Molecular analysis was performed in 83.3% of cases, with FLT3 mutations being the predominant finding. According to the ELN 2017 risk classification, most patients were categorized as intermediate risk. These results support the use of intensive treatment in favorable clinical-biological contexts and are consistent with the observations of Döhner et al. regarding risk distribution in elderly patients [20–22].

Induction therapy achieved a complete remission rate of 54.2%, with early mortality at 14.6%, commonly due to infections, hemorrhagic events, or thrombosis. Therapeutic response was more frequent in patients with ECOG 0–1, CCI <3, and HCT-CI <2. Conversely, a higher number of comorbidities, HCT-CI scores ≥3, and prolonged PT were associated with lack of response and increased risk of early death. These findings are consistent with the results reported by Cortes, Mehta, and Aydin regarding the predictive value of clinical scores in AML [23,24].

Disease relapse was frequent, including among patients who achieved complete response, with a progression rate of 75% and a time to progression under 6 months in most cases (69.6%). Progression-free survival (PFS) had a median of 10 months, and multivariate analysis identified prolonged progression time (PT) as an independent predictor of progression (HR = 2.30; p = 0.043). Although MRD was assessed in a limited number of patients, the persistence of molecular disease correlated with an increased risk of relapse. These findings confirm recent observations by Juga, Kusuda, Walter, and Heuser, highlighting the role of PT and MRD as predictive markers in AML [25–29].

Overall survival analysis showed a median of 11 months and an estimated mean duration of 14.4 months (95% CI: 10.2–18.5 months), with a mortality rate of 90% at the time of evaluation. In the multivariate model, survival was significantly influenced by clinical scores: CCI ≥3 (HR = 2.16, p = 0.012), HCT-CI ≥2 (HR = 2.01, p = 0.022), and ECOG 0–1 (HR = 0.58, p = 0.034). These results confirm the role of functional scores and comorbidities in the prognosis of elderly AML patients. According to data published by Sorror et al., the HCT-CI score is a significant predictor of mortality in this population [30]. Thus, rigorous clinical evaluation—including scores such as CCI, HCT-CI, and ECOG—

not only guides therapeutic selection but also provides valuable information regarding long-term survival [30].

The limitations of our study warrant a cautious interpretation of the results. The retrospective design, conducted in a single center and involving a relatively small number of patients, reduces the generalizability of the conclusions. Moreover, molecular analysis was not completed in all cases, and MRD assessment was available only for a limited subset of patients. Although treatment selection followed guideline recommendations, it was also influenced by clinical context and resource availability, reflecting the inherent variability of real-world practice [30].

Studies conducted outside of controlled trials show that, in real-life settings, elderly patients with AML often present with multiple comorbidities, and therapeutic decisions are frequently based on a delicate balance between efficacy and tolerability [31]. Even under these conditions, the data obtained help to outline a profile of elderly patients who may benefit from intensive treatment when selection is based on an integrated assessment of functionality and biological risk.

4.2. Study 2 – Analysis of the Evolution of Patients Treated with Hypomethylating Agents in Monotherapy or in Combination with Venetoclax

The second study involved 82 patients diagnosed with acute myeloid leukemia (AML) between 2017 and 2023, who were treated at the Colțea Hematology Clinic. These patients received hypomethylating agents—either Azacitidine or Decitabine—either as monotherapy or in combination with Venetoclax. The treatment plan was customized based on each patient's clinical profile and available therapies.

All participants were deemed ineligible for intensive chemotherapy due to criteria such as poor functional status, advanced age, and multiple comorbidities, with no upper age limit imposed. Notably, 45.1% of the patients were over 75 years old, and there was no significant age difference compared to those aged 65–74 years ($p = 0.377$). The cohort predominantly consisted of men (63.4%), a finding that was statistically significant ($p = 0.015$). Additionally, 84.1% of the patients were from urban areas ($p = 0.001$).

Cytogenetic and molecular investigations facilitated prognostic stratification in 78 cases (89.6%) according to ELN 2017. Cytogenetic evaluation was available for half of these

cases (41 patients, 50.0%), indicating an adverse karyotype in 19 cases (46.4%), an intermediate karyotype in 21 cases (51.2%), and a favorable karyotype in only one case (2.4%). This distribution showed a statistically significant difference ($\chi^2 = 17.76$; $p < 0.001$).

Molecular testing was conducted on 49 patients (59.8%), with 45 cases (91.8%) categorized as intermediate molecular risk and only 3 patients (6.2%) in the favorable group. A total of 5 patients (10.2%) had documented mutations (FLT3-ITD, RUNX1-RUNX1T1, JAK2), with a significant difference observed between mutated and non-mutated cases ($\chi^2 = 31.04$; $p < 0.001$). Compared to the previous study, the proportion of patients with a favorable risk profile was very low, indicating a more adverse biological background. Commonly associated comorbidities included cardiovascular diseases (in over 60% of cases), chronic pulmonary diseases, and chronic kidney disease. These findings underscore the severity of the initial condition in patients treated with hypomethylating agents, characterized by a vulnerable functional and biological profile. This situation justifies the use of better-tolerated therapeutic regimens that may exhibit increased efficacy when combined with Venetoclax.

Discussion

In the evaluated cohort, Decitabine was the most commonly used hypomethylating agent as first-line therapy, and its efficacy was comparable to that of Azacitidine (46.9% vs. 50%), with no statistically significant difference. However, more than half of the patients did not achieve a hematologic response, highlighting the limitations of current therapeutic options for this frail patient population and emphasizing the need for regimens with improved efficacy [32].

Specialized literature supports the observations from our cohort, indicating similar response rates between Azacitidine and Decitabine. A multicenter retrospective study reported an overall response rate of 32% for Azacitidine and 39.5% for Decitabine, without statistical significance ($p = 0.12$) [32]. Likewise, a recent meta-analysis showed comparable values (38% vs. 40%; $p = 0.825$), reinforcing the notion that both therapies exhibit a similar efficacy profile in treating AML in elderly patients [33].

Overall, both Decitabine and Azacitidine proved to be therapeutic options with comparable efficacy in the initial treatment of elderly patients with acute myeloid leukemia (AML). Nevertheless, the high proportion of cases without a hematologic response

underscores the limitations of these monotherapies. It supports the need for developing combined or personalized therapeutic strategies tailored to each patient's profile [32,33].

The absence of a significant therapeutic response was prevalent among patients with poor functional status and multiple comorbidities, confirming the vulnerability of this subgroup. Other real-world analyses support our results: Filì et al. reported an overall response rate of only 33% for Decitabine in elderly patients with AML [34], while in the study by Chen et al., the overall response rate for hypomethylating agents used as monotherapy was 48.6% [35]. Moreover, Kwag et al. observed even lower efficacy, with a response rate of 24.3% for Decitabine monotherapy [36]. All these findings converge toward the conclusion that, for frail patients, hypomethylating monotherapy is often insufficient, and therapeutic options must be expanded by including targeted agents or sequential treatment strategies [34–36].

In our analysis, patients treated exclusively in first-line therapy had a median overall survival of 7 months, whereas those who also received a second-line treatment reached a median survival of 11 months—a statistically significant difference in favor of sequential therapy ($p = 0.035$). This disparity may reflect the natural selection of cases with slower disease progression and better functional status, but it also supports the potential benefit of continuing treatment in eligible patients.

Our findings align with those reported in the literature. Lessi et al. described a median survival of 12.3 months for secondary AML and 6.1 months for de novo forms treated with hypomethylating agents in subsequent lines [37]. In a real-world analysis, Hoff and colleagues reported a median survival of 13 months for elderly patients receiving first-line HMA-Venetoclax therapy [38]. Similarly, DiNardo et al. reported a median survival of 17.5 months for de novo AML in an early clinical trial involving the same combination [39]. The differences compared to results from controlled clinical trials may be attributed to the high variability of patient populations in routine practice, where high-risk cytogenetic profiles and multiple comorbidities are more common, reflecting a more complex clinical reality [37–39].

Extending treatment in carefully selected subgroups may offer a real survival benefit, even in the absence of a complete response after first-line therapy. This highlights the essential role of continuous reassessment of clinical and biological status to identify patients who may benefit from an extended therapeutic approach, regardless of the initial apparent response [37,38]. Although complete hematologic response was used as the primary

indicator of efficacy, some patients in the analyzed cohort, despite lacking documented remission, demonstrated stable mid-term evolution, especially after initiating second-line treatment with Venetoclax. This suggests a potential biological control of the disease, even in the absence of classical morphological remission. In such cases, incorporating minimal residual disease (MRD) assessment and other functional markers could provide deeper insight into the true therapeutic effectiveness, particularly in frail patients or those with reduced hematopoietic reserves [38,39].

In our analysis, more than half of the patients treated with the hypomethylating agent–Venetoclax combination (53.3%) achieved red blood cell transfusion independence, compared to only 18.8% in the Decitabine group and 8.3% in the Azacitidine group. The differences were statistically significant ($p = 0.011$), suggesting a clear functional advantage in favor of the combined regimen. These results are consistent with data published by DiNardo et al., who reported a transfusion independence rate of 37.5% for the Azacitidine–Venetoclax combination versus 16.9% for monotherapy [40]. Similarly, Hoff et al. confirmed in a real-world analysis the effectiveness of this regimen, which was associated with faster hematologic recovery and prolonged survival [38]. Additionally, an expanded access study conducted in Japan by Asada and colleagues showed that the Venetoclax–LDAC combination may offer a favorable safety profile and notable hematologic response, supporting the potential of this approach in clinical practice [41]. Although in our cohort, monotherapy with LDAC was associated with a lack of response and increased early mortality, literature data suggest that in selected subgroups, the LDAC–Venetoclax regimen could represent a viable alternative [38,40,41].

Early mortality (within the first 60 days from treatment initiation) was 21.6%, predominantly due to severe infections, followed by cardiovascular and hemorrhagic complications. The highest rate was observed among patients treated with LDAC monotherapy, particularly in second-line settings (7 out of 8 deaths). These findings reflect the biological frailty of a subset of the cohort. According to a Swedish study, active treatments reduce early mortality in elderly AML patients [42], and Hoff et al. reported a 60-day mortality rate of 17% with the HMA-Venetoclax regimen [38].

Patients who responded favorably to treatment were often under 75 years old, had an ECOG score of 0–1, normal cardiac function, and a low Charlson comorbidity index. These characteristics define a subgroup with a good functional reserve and a more favorable prognosis. These findings are supported by the multicenter European study published by

Molica et al., which identified the same factors as predictors of survival and response to hypomethylating agents [10].

Overall, the treatment was well tolerated. No patient required permanent discontinuation due to toxicity. The most common complications were persistent cytopenias and recurrent infections, particularly among patients with poor functional status or limited hematopoietic reserve. Although adverse event documentation was incomplete, the safety profile was comparable to that described in similar cohorts.

Cytogenetic and molecular assessment enabled prognostic stratification of patients using methods such as conventional karyotyping, FISH, and analysis of recurrent mutations. Most cases showed an unfavorable risk profile, though some patients had intermediate or standard risk. The lack of full access to extended testing (e.g., NGS) in certain situations limited the ability to correlate genetic abnormalities with treatment response precisely. Nevertheless, the data reflect the realities of a regional center, highlighting the importance of genetic evaluation at diagnosis.

A lack of therapeutic response was frequently associated with adverse cytogenetic abnormalities, an HCT-CI score of 3 or higher, and poor functional status (ECOG score of 2 or higher). A complex karyotype or the presence of multiple abnormalities suggests intrinsic resistance to hypomethylating therapy. These findings may help identify patients who are refractory early and support the selection of alternative therapeutic strategies, including combination regimens.

This study offers a realistic perspective on the use of hypomethylating agents, including Venetoclax, in elderly patients ineligible for intensive treatments. Survival and therapeutic response were influenced by clinical factors (age, ECOG) and biological factors (hematologic reserve, cytogenetic profile). Limited access to advanced investigations, such as next-generation sequencing (NGS) testing, reduced the capacity for molecular stratification. The results support the need for integrated assessment at diagnosis and the development of clinical-biological algorithms to personalize therapeutic strategies.

4.3. The Impact of Therapeutic Strategy on the Prognosis of Elderly Patients with AML: Intensive Chemotherapy vs. HMA ± Venetoclax

A comparison of the two cohorts included in the study revealed significant differences in clinical and hematological profiles, with direct implications for therapeutic selection and disease monitoring in elderly patients with acute myeloid leukemia (AML).

4.4. General Conclusions

Based on the comparative analysis of the two studied cohorts, the following general conclusions were formulated, with direct relevance for current hematology practice and therapeutic decision-making in elderly AML patients:

In the cohort treated with intensive chemotherapy:

- Patients eligible for this treatment were significantly younger ($p < 0.001$), had good functional status (ECOG 0–1; $p = 0.004$), and had lower Charlson Comorbidity Index (CCI) scores ($p = 0.002$).
- The complete remission rate was higher compared to the non-intensive cohort (63% vs. 39%; $p = 0.012$), and the median overall survival reached 11 months, significantly longer than in the comparative group ($p = 0.042$).
- Progression-free survival (PFS) was also significantly improved ($p = 0.03$) despite a higher relapse rate ($p = 0.04$).

Other favorable or unfavorable prognostic factors identified in this group:

- Age <75 years and preserved cardiac function were associated with better prognosis.
- ECOG 0–1 correlated with favorable response ($p < 0.05$).
- HCT-CI scores ≥3, ECOG ≥2, and adverse karyotype were significantly associated with lack of therapeutic response ($p < 0.05$).
- The persistence of measurable residual disease (MRD) was linked to early relapse.
- Prolonged prothrombin time (PT) correlated with an increased risk of relapse and early mortality.
- Continuing therapy, even in the absence of complete remission, provided an absolute survival benefit.

In the cohort treated with hypomethylating agents ± Venetoclax:

- The combination treatment with HMA-Venetoclax showed better tolerability and a significantly higher rate of transfusion independence (53.3% vs. 18.8% with Decitabine monotherapy; $p = 0.011$).
- Overall tolerability was acceptable, with no permanent discontinuations due to toxicity.
- Early mortality did not differ significantly between groups. Still, it was particularly high among patients treated with LDAC monotherapy as second-line therapy, where 7 out of 8 patients died without achieving a therapeutic response.

Characteristics associated with increased treatment efficacy in this group:

- Patients under 75 years of age, with an ECOG score of 0–1 and preserved cardiac function, achieved better therapeutic responses ($p < 0.05$).
- Transfusion independence proved to be a useful functional marker, more frequently achieved in combination regimens.
- Continuation of treatment into a second line provided a significant survival benefit, even in the absence of an initial complete response.
- Adverse cytogenetic profiles and poor functional status were associated with a lack of response, similar to the cohort receiving intensive chemotherapy.

5. Personal Contributions

I conducted a rigorous comparative analysis of two cohorts of elderly patients diagnosed with AML, differentiated by their eligibility for intensive chemotherapy, to highlight the impact of each therapeutic strategy on survival, hematologic response, and treatment tolerability.

I identified the clinical and biological factors associated with prognosis in both cohorts by correlating ECOG, CCI, and HCT-CI scores, as well as the genetic profile (including karyotype and recurrent mutations), with the likelihood of response and survival, thus contributing to the development of a risk profile applicable in clinical practice.

I integrated real-world data into a prognostically relevant statistical analysis, validating previously reported findings from international studies and highlighting the specific

characteristics of a population treated in a regional center under conditions of unequal access to advanced genetic testing.

I evaluated the impact of hypomethylating treatment combined with venetoclax on transfusion independence and progression-free survival, identifying a significant benefit in selected subgroups of patients with preserved cardiac function and good performance status in the absence of major contraindications.

I developed a model for the integrated interpretation of clinical, biological, and therapeutic response data, with practical applicability in guiding treatment decisions for elderly AML patients, particularly in the context of real-life limitations related to tolerability and multiple comorbidities.

During the completion of this doctoral thesis, I published three scientific articles in internationally indexed journals, building upon the data and conclusions drawn from my research. The first article, a review published in the *Journal of Clinical Medicine*, addressed FLT3 inhibitors in AML, consolidating the theoretical and bibliographic foundations of the general section. The second article, published in *Hematology Reports*, analyzed the impact of comorbidities on therapeutic decisions and clinical outcomes in elderly AML patients, supporting the analysis included in Chapter 5 of the thesis. The third article, published in *Cureus*, presented our center's experience regarding the efficacy of hypomethylating agents ± Venetoclax, corresponding to the data detailed in Chapter 6.

I was directly involved in defining the scientific objectives, collecting and interpreting the data, as well as writing and publishing each article. These contributions reflect my academic journey and strengthen the scientific relevance of this thesis by integrating the obtained results into the context of current international research on the treatment of acute myeloid leukemia in the elderly.

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List of Published Scientific Papers

1. **Cristina Negotei,** Andrei Coliță, Iuliana Mitu, Anca Roxana Lupu, Mihai-Emilian Lăpădat, Constanța Elena Popovici, Mihaela Crăinicu, Oana Stanca, Nicoleta-Mariana Berbec – A Review of FLT3 Kinase Inhibitors in AML. Journal of Clinical Medicine, 2023; 12(20):6429. FI 3.9 (Clarivate 2023), https://doi.org/10.3390/jcm12206429
2. **Cristina Negotei,** Iuliana Mitu, Silvana Angelescu, Florentina Grădinaru, Cristina Mambet, Oana Stanca, Mihai-Emilian Lăpădat, Cristian Barta, Georgian Halcu, Carmen Săguna, Aurora Arghir, Mihaela-Sorina Papuc, Andrei Turbatu, Nicoleta-Mariana Berbec, Andrei Coliță – Incorporation of a Comorbidity Index in Treatment Decisions for Elderly AML Patients Can Lead to Better Disease Management—A Single-Center Experience. Hematology Reports, 2024; 16(4):781–794. FI 1.1 (Clarivate 2023), Capitolul 5, pag. 37-64. https://doi.org/10.3390/hematolrep16040074
3. **Cristina Negotei**, Iuliana Mitu, Silvana Angelescu, Oana Stanca, Nicoleta-Mariana Berbec, Cristian Barta, Mihai-Emilian Lăpădat, Andrei Coliță – The Effectiveness of Hypomethylating Agents in Elderly Patients With Acute Myeloid Leukemia: Insights From a Single-Center Experience. Cureus, 2025; 17(4): e82957. Indexată în PubMed Central, Capitolul 6, pag. 71-94 https://doi.org/10.7759/cureus.82957