

# Dual Growth Factor (rhTPO + G-CSF) and Chemotherapy Combination Regimen for Elderly Patients with Acute Myeloid Leukemia: A Phase II Single-Arm Multicenter Study

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**Abstract:** Acute myeloid leukemia (AML) is a disease affecting older adults, although optimal strategies for treating such patients remain unclear. This prospective phase II, open-label, multicenter study was designed to assess the efficacy and safety of two hematologic growth factors, recombinant human thrombopoietin (rhTPO) and granulocyte colony-stimulating factor (G-CSF), in combination with decitabine, cytarabine, and aclarubicin (D-CTAG regimen) to treat older adults with newly diagnosed AML (Identifier: NCT04168138). The above agents were administered as follows: decitabine (15 mg/m<sup>2</sup> daily, days 1–5); low-dose cytarabine (10 mg/m<sup>2</sup> q12 h, days 3–9); rhTPO (15,000 U daily, days 2, 4, 6, 8, 10–24 or until >50×10<sup>9</sup>/L platelets); aclarubicin (14 mg/m<sup>2</sup> daily, days 3–6); and G-CSF (300 µg daily, days 2–9). We concurrently monitored historic controls treated with decitabine followed by cytarabine, aclarubicin, and G-CSF (D-CAG) only. After the first D-CTAG cycle, the overall response rate (ORR) was 84.2% (16/19), including 13 (73.7%) complete remissions (CRs) and three (15.8%) partial remissions. This CR rate surpassed that of the D-CAG treatment ( $p < 0.05$ ). Median overall survival (OS) time in the D-CTAG group was 20.2 months (range, 4–31 months), compared with 14 months in the D-CAG group, and 1-year OS was 78%. The proportion of those experiencing grade III–IV thrombocytopenia was significantly lower for D-CTAG (57.9%) than for D-CAG (88.4%;  $p < 0.05$ ). Ultimately, the curative effect of adding rhTPO was not inferior to that of D-CAG, and D-CTAG proved safer for elderly patients, especially in terms of hematologic toxicity. A prospective phase III randomized study is warranted to confirm these observations.

**Keywords:** rhTPO, elderly, acute myeloid leukemia, CAG, decitabine

## Introduction

Acute myeloid leukemia (AML) is one of the most common hematologic malignancies and affects older adults. The median age at diagnosis is 67 years. As the elderly increasingly account for a greater population percentage, AML is becoming more problematic. During the past 30 years, outcomes have improved for younger patients, whereas the prospects for older adults (> 60 years) have remained poor.<sup>1</sup> The response rate in older adults given standard induction regimens is < 50%, and median overall survival (OS) is < 1 year.<sup>2–4</sup> Older adults elderly are also inordinately burdened by unfavorable cytogenetic defects, medical comorbidities, and reduced tolerability to intensive chemotherapeutic protocols. These vulnerabilities

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predispose older adults to poorer outcomes than their younger counterparts, conferring lower response rates and shortened survival times (progression-free and overall survival [OS]).<sup>5</sup> Safe and effective treatments for elderly patients with AML are thus urgently needed.

In 2000, Saito et al introduced a regimen of granulocyte colony-stimulating factor (G-CSF) plus low-dose cytarabine (ara-C) and aclarubicin (ACR) for use in this setting (CAG regimen),<sup>6</sup> in an attempt to incorporate a hematologic growth factor in AML induction therapy, rather than relying on supportive care. The addition of decitabine, a demethylation agent, further improved the prognosis, yielding a 10-month median OS.<sup>7</sup> This successful use of G-CSF in an induction regimen for AML confirmed its utility, helping to increase efficacy and reduce side effects in elderly patients.

Thrombopoietin (TPO) is a major factor in regulating megakaryocytic proliferation, maturation, and platelet formation.<sup>8</sup> Recombinant human TPO (rhTPO) has been approved by China's State Food and Drug Administration to treat thrombocytopenia after chemotherapy. TPO and c-MPL receptors are also involved in various physiologic processes, such as mitigating myocardial injury, nerve repair, vascular regeneration, sex hormone secretion, and immune regulation.<sup>9</sup> However, the role of rhTPO in an induction regimen for AML is unreported as yet.

To determine if adding rhTPO to D-CAG (G-CSF) will increase the overall response rate (ORR) while decreasing the side effect of toxic agents, we designed a regimen of rhTPO and G-CSF in combination with decitabine, cytarabine, and aclarubicin (D-CTAG regimen). This trial aimed to determine the safety and efficacy of this

D-CTAG regimen as a treatment for older adult patients with newly diagnosed AML.

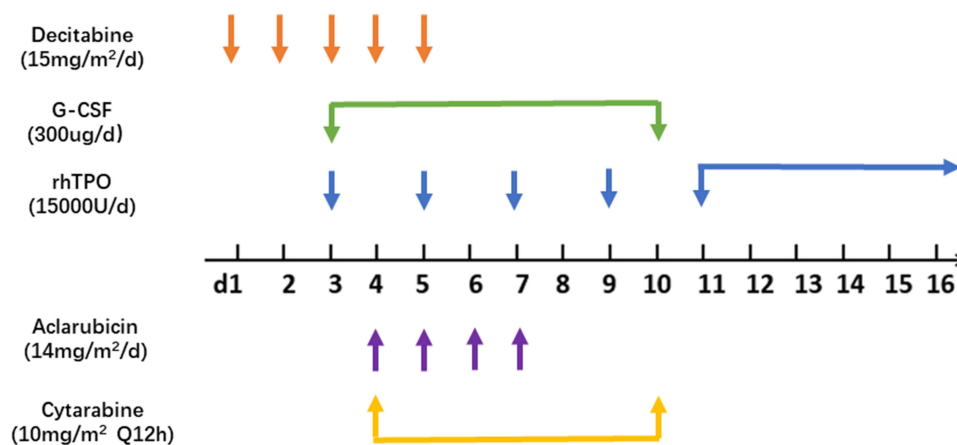
## Materials and Methods

### Patients and Treatment

This was an investigator-initiated, prospective, nonrandomized, single-arm phase II clinical trial in elderly patients with AML registered at [www.clinicaltrials.org](http://www.clinicaltrials.org) (Identifier: NCT04168138). Candidates for the test regimen were elderly patients (> 60 years) newly diagnosed with AML, excluding those with acute promyelocytic leukemia or a chronic myeloid leukemic blast crisis. Eastern Cooperative Oncology Group performance status of 0–3 was further required.

This study was approved by the Human Ethics Committee of the China Medical University at Shengjing Hospital, and written informed consent was granted by all participants. This study was conducted in accordance with the Declaration of Helsinki.

The D-CTAG chemotherapeutic induction regimen consisted of decitabine (15 mg/m<sup>2</sup> daily, days 1–5); low-dose cytarabine (10 mg/m<sup>2</sup> q12 h, days 3–9); rhTPO (15,000 U daily, days 2, 4, 6, 8, and 10–24 or until a platelet count > 50 × 10<sup>9</sup>/L was observed); aclarubicin (14 mg/m<sup>2</sup> daily, days 3–6); and G-CSF (300 µg daily, days 2–9; Figure 1). We also collected data on a comparable patient group given traditional D-CAG chemotherapy without rhTPO (decitabine 15 mg/m<sup>2</sup> daily, days 1–5; low-dose cytarabine 10 mg/m<sup>2</sup> q12 h, days 3–9; aclarubicin 14 mg/m<sup>2</sup> daily, days 3–6; G-CSF 300 µg daily, days 2–9) at the same time clinically to compare therapeutic outcomes. We evaluated the response after the first course of treatment. If the patient can tolerate and reach PR or above, continue D-CTAG



**Figure 1** Schematic of the D-CTAG treatment regimen for AML.

chemotherapy and up to six courses. After this, the patient received decitabine monotherapy to maintain the disease until its progression. If patients stop the D-CTAG regimen for > 6 months and relapse, they can restart the D-CTAG regimen, enter clinical trials, or consider treatment with azacitidine or B-cell leukemia/lymphoma-2 inhibitors.

Treatment responses were assessed according to the National Comprehensive Cancer Network clinical practice guidelines of AML (version 2.2019). The ORR was defined as the rates of complete and partial remissions (CR; PR). Toxicities were determined according to the National Cancer Institute Common Toxicity Criteria.

## Statistical Analysis

Differences in continuous variables were analyzed using t-tests and chi-squared tests. Kaplan-Meier analysis was performed to estimate the survival probabilities. The statistical analysis of all study data was driven by standard software (SPSS 22.0; IBM Corp, Armonk, NY, USA), setting significance at  $p < 0.05$ .

## Results

### Patient Characteristics

Between January 2017 and May 2020, 19 willing patient participants (age range, 61–81 years) with newly diagnosed AML were recruited for this trial of D-CTAG. A summary of patient characteristics is provided in Table 1. Six of these patients had also developed secondary malignant tumors. To assess the potential merit of added rhTPO, we concurrently monitored 38 patients treated with D-CAG only as controls. The baseline characteristics of the two therapeutic groups (D-CTAG vs D-CAG) were similar (Table 1).

### Therapeutic Responses and Survival

After the first cycle, the D-CTAG induction regimen yielded an ORR of 84.2% (16/19), including 13 (73.7%) CRs and three (15.8%) PRs. In controls receiving D-CAG, the ORR was 78.9% (30/38), with 23 (60.5%) CRs and seven (18.4%) PRs. Although the CR rate for D-CTAG was significantly higher than D-CAG ( $p < 0.05$ ), broader patient samplings are needed for verification.

During a median follow-up of 31 months, the median overall survival (OS) time was 20.2 months (range, 4–31 months) in the D-CTAG group (Figure 2). All patients were followed for at least 1 year, with an OS of 78%. Again, OS in the D-CTAG group exceeded that of the D-CAG group (median OS, 14 months; Figure 3).

**Table 1** Clinical Characteristics of the Patient Population

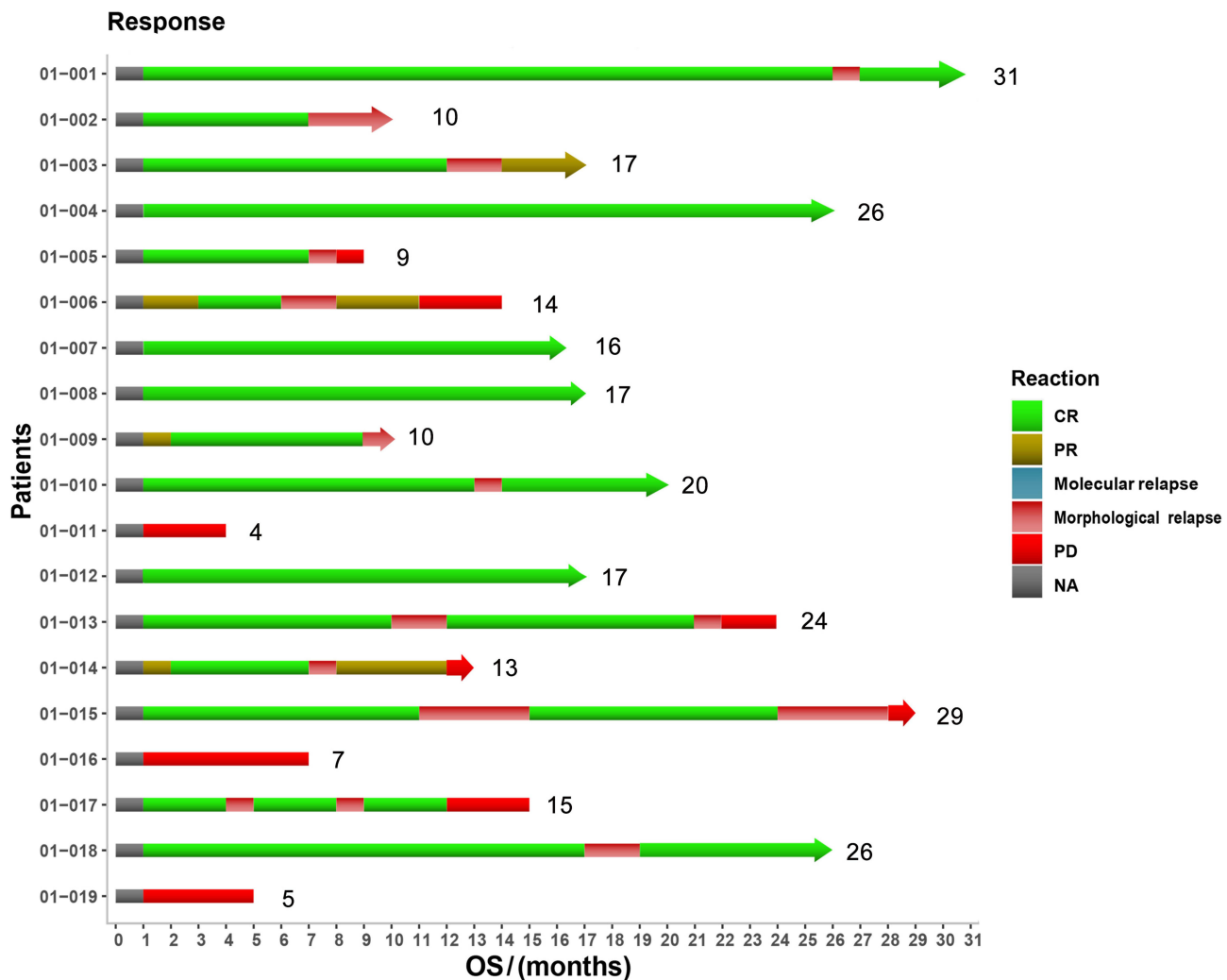
|  | D-CTAG (n = 19) | D-CAG (n = 38) | P-value |
|--|-----------------|----------------|---------|
| Age, years (mean, range)                   | 70 (61–81)      | 69 (60–80)     | > 0.05  |
| Gender (n, %)                              |                 |                | > 0.05  |
| Male                                       | 7 (36.8)        | 16 (42.1)      |         |
| Female                                     | 12 (63.2)       | 22 (57.9)      |         |
| FAB AML classification (n, %)              |                 |                | > 0.05  |
| AML-M1                                     | 1 (5.3)         | 3 (7.9)        |         |
| AML-M2                                     | 8 (42.1)        | 17 (44.7)      |         |
| AML-M4                                     | 4 (21.0)        | 7 (18.4)       |         |
| AML-M5                                     | 6 (31.6)        | 11 (28.9)      |         |
| ECOG (n, %)                                |                 |                | > 0.05  |
| 0–1  | 14 (73.7)       | 27 (71.0)      |         |
| 2–3  | 5 (26.3)        | 11 (29.0)      |         |
| NCCN risk stratification (n, %)            |                 |                | > 0.05  |
| Low risk                                   | 5 (26.3)        | 8 (21.0)       |         |
| Intermediate risk                          | 8 (42.1)        | 19 (50)        |         |
| High risk                                  | 6 (31.6)        | 11 (29)        |         |
| WBC ( $\times 10^9/L$ ; mean, range)       | 20 (0.5–60)     | 22 (1.0–78)    | > 0.05  |
| Hemoglobin (g/L; mean, range)              | 68 (43–101)     | 70 (50–110)    | > 0.05  |
| Platelets ( $\times 10^9/L$ ; mean, range) | 57 (4–220)      | 42 (6–270)     | > 0.05  |
| Mutation (n, %)                            |                 |                | > 0.05  |
| DNMT3A                                     | 6 (31.5)        | 9 (23.7)       |         |
| TET2                                       | 4 (21.0)        | 15 (39.5)      |         |
| IDH1                                       | 2 (10.5)        | 3 (7.9)        |         |
| IDH2                                       | 1 (5.3)         | 6 (15.8)       |         |
| ASXL1                                      | 3 (15.8)        | 4 (10.5)       |         |
| NPM1                                       | 3 (15.8)        | 8 (21.1)       |         |
| CEBPA                                      | 4 (21.0)        | 9 (23.7)       |         |
| FLT3                                       | 4 (21.0)        | 6 (15.8)       |         |
| KIT  | 5 (26.3)        | 11 (28.9)      |         |
| TP53                                       | 3 (15.8)        | 5 (13.2)       |         |

**Note:** Data are expressed as number (%) or median (range).

**Abbreviations:** D-CTAG, decitabine, low-dose cytarabine, recombinant human thrombopoietin, aclarubicin, and granulocyte colony-stimulating factor; D-CAG, decitabine, low-dose cytarabine, aclarubicin, and granulocyte colony-stimulating factor; FAB, French–American–British; ECOG, Eastern Cooperative Oncology Group; NCCN, National Comprehensive Cancer Network.

### Treatment-Related Toxicity

All recipients of D-CTAG or D-CAG were observed for thrombocytopenia and neutropenia. The proportion of those experiencing grade III–IV thrombocytopenia was significantly lower for D-CTAG (57.9%) than for



**Figure 2** Efficacy and survival in patients given the D-CTAG regimen.

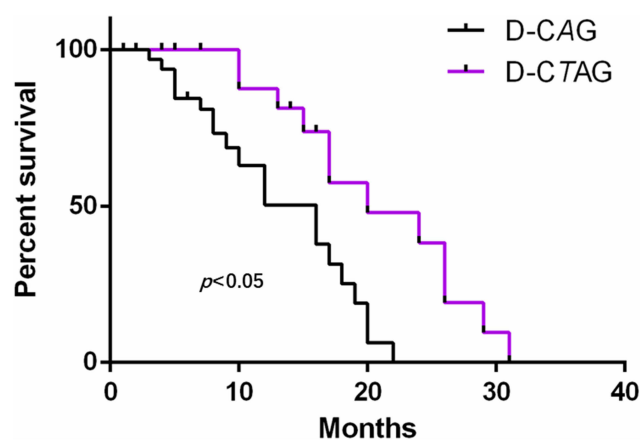
D-CAG (88.4%;  $p < 0.05$ ; Table 2). The D-CTAG group also exhibited earlier hematologic recovery than the D-CAG group. Median times to recovery of neutrophils were 9.6 days and 11.1 days, respectively ( $p < 0.05$ ). In terms of platelet recovery, median times were 8.9 days and 13.2 days, respectively ( $p < 0.05$ ), and the mean number of required platelet transfusions was significantly less for those receiving D-CTAG than D-CAG ( $3.2 \pm 0.3$  vs  $9.9 \pm 1.8$ ;  $p < 0.05$ ). Hence, it appears that rhTPO reduces hematologic toxicity.

## Discussion

The CAG priming regimen launched by Saito et al in 2000 constituted the first use of a cellular growth factor (G-CSF) in AML treatment.<sup>6</sup> The incorporation of G-CSF served to shorten neutropenic intervals, reduce the incidence of serious infection, and lower mortality. Leukemic cells were

driven to enter the cell cycle, thus enhancing the efficacy of S-phase-specific cytotoxic drugs (eg, ara-C). Despite concerns that G-CSF might promote leukemic cell growth, many years of clinical practice have since proven that CAG-based chemotherapy is safe and effective for elderly patients with leukemia or relapsed refractory leukemia.<sup>10</sup>

This successful application of G-CSF in treating AML encouraged us to explore the addition of other hematopoietic growth factors. Once bound to its specific c-MPL receptor, TPO activates a series of downstream signaling pathways, such as Janus kinase/signal transducer and activator of transcription phosphatidylinositol-3-kinase/protein kinase B, and Ras/mitogen-activated protein kinase. Aside from megakaryocytic maturation and differentiation,<sup>11</sup> TPO is implicated in various physiologic events, including mitigation of myocardial injury, nerve repair, angiogenesis, sex hormone secretion, and immune



**Figure 3** Survival curves of the D-CTAG and D-CAG regimens.

regulation;<sup>9</sup> and it is generally acknowledged that rhTPO may alleviate chemotherapy-induced thrombocytopenia in patients with solid tumors. However, there has been no broad usage of rhTPO in AML chemotherapy, perhaps because c-MPL receptors are primarily limited to surfaces of hematopoietic stem cells, progenitor cells, megakaryocytes, and platelets.

Whether rhTPO is truly capable of AML propagation has always been in doubt. However, pertinent publications on c-MPL receptors have shown no evidence that leukemic disease is intensified. Chelvatheebam et al<sup>9</sup> stratified patients with AML by age, gender, FAB type, karyotype, and long-term survival rate, finding no correlation with c-MPL receptor expression. In the context of AML, a positive correlation between c-MPL receptor expression and high-level expression of CD34+ has been documented

by Ayala et al,<sup>12</sup> but long-term and disease-free survival were both unrelated. Hence, c-MPL receptor expression in patients with AML has no clear bearing on prognosis.

In observing 108 patients with AML (no M3 or M7 variants), Archimbaud et al<sup>13</sup> determined that leukemic stimulatory effect due to Pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF), a c-MPL receptor agonist, was lacking. Schiffer et al<sup>14</sup> also studied 57 patients with relapsed AML (no M3 or M7 variants), recording similar CR rates and survival times in patients given PEG-rHuMGDF or a placebo. These results indicate that PEG-rHuMGDF has no obvious *in vivo* proliferative effect on leukemic cells and provide an indirect theoretical basis for the use of rhTPO, another c-MPL receptor agonist.

With the emergence of molecularly targeted drugs, senile myeloid leukemia has also made some progress recently. Phase 1/2 studies of venetoclax combined with AZA, DEC, or LDAC in newly diagnosed patients unfit for intensive induction chemotherapy showed very respectable CR/CRi rates of 54–67%. Side effects were notable for significant myelosuppression, neutropenic fevers and other infections.<sup>15</sup> In this study, the application of dual growth factors is of great significance for reducing the side effects of neutropenia and thrombocytopenia, enabling older adults to better tolerate the treatment and achieve a more favorable response.

We designed the D-CTAG regimen to assess rhTPO as an added treatment for AML in older adults. Ultimately, D-CTAG recipients achieved an ORR of 84.2%, showing a significantly higher CR rate (73.7%) than those given D-CAG only (60.5%;  $p < 0.05$ ). The OS in the D-CTAG

**Table 2** Adverse Events During Induction Therapy

| Grade                      | D-CTAG   |           | D-CAG     |           |
|----------------------------|----------|-----------|-----------|-----------|
|                            | I-II     | III-IV    | I-II      | III-IV    |
| Hematologic toxicities     |          |           |           |           |
| Neutropenia                | 6 (31.6) | 13 (68.4) | 7 (20.6)  | 27 (79.4) |
| Thrombocytopenia           | 8 (42.1) | 11 (57.9) | 4 (11.6)  | 30 (88.4) |
| Neutropenic fever          | 4 (21.1) | 15 (78.9) | 5 (14.8)  | 29 (85.2) |
| Non-hematologic toxicities |          |           |           |           |
| Hepatobiliary disorders    | 4 (21)   | 0         | 6 (17.6)  | 0         |
| Nausea, vomiting           | 6 (31.6) | 0         | 10 (29.4) | 0         |
| Mucositis                  | 6 (31.6) | 0         | 15 (44.1) | 0         |
| Cardiac disorders          | 4 (21.1) | 0         | 9 (26.4)  | 1 (2.9)   |

**Note:** All data are expressed as number (%).

**Abbreviations:** D-CTAG, decitabine, low-dose cytarabine, recombinant human thrombopoietin, aclarubicin, and granulocyte colony-stimulating factor; D-CAG, decitabine, low-dose cytarabine, aclarubicin, and granulocyte colony-stimulating factor.

group (median, 20.2 months) also exceeded that in the D-CAG group (median, 14 months) and was far greater than the even lower OS (median, 10 months) reported by others after D-CAG therapy.<sup>16–19</sup> The D-CTAG regimen should thus be quite effective in this patient demographic, proving non-inferior to D-CAG alone. Greater safety was afforded these elderly patients as well. Compared with our standard D-CAG protocol, D-CTAG therapy was less fraught with grade III–IV thrombocytopenia and brought earlier hematologic recovery, resulting in fewer required platelet transfusions. In the future, a prospective phase III randomized study is warranted to gauge the efficacy and safety of D-CTAG in a larger patient sample and validate this novel therapeutic modification for older adults with AML.

## Conclusion

The curative effect of adding rhTPO was not inferior to that of D-CAG, and D-CTAG proved safer for older adults, especially in terms of hematologic toxicity. D-CTAG is a safe and effective treatment plan for older adults with AML.

## Ethics Approval and Consent to Participate

The studies involving patients were approved by The Ethics Committee of Shengjing Hospital of China Medical University. The participants provided their written informed consent to participate in this study. This study was conducted in accordance with the Declaration of Helsinki.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was supported by the Natural Science Foundation of Liaoning Province (201800875).

## Disclosure

The authors declare that they have no competing interests.

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