Technology in Cancer Research & Treatment
Volume 24: 1-8

DOI: 10.1177/15330338241312436
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Pegylated Liposomal Doxorubicin Combined with Cytarabine and Granulocyte Colony-Stimulating Factor for Treating Newly Diagnosed Older and Unfit Acute Myeloid Leukemia Patients: A Prospective, Single-Center, Single-arm, Phase II Study

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Abstract

Background: Effective treatment options are limited for elderly patients with acute myeloid leukemia (AML). A prospective phase II study was conducted to investigate the safety and efficacy of pegylated liposomal doxorubicin (PLD) combined with low-dose cytarabine (LDAC) and granulocyte colony-stimulating factor (G-CSF) in newly diagnosed older and unfit AML patients. **Methods:** Twenty-two patients were enrolled and deemed evaluable. The study included one cycle of induction and four cycles of consolidation, followed by maintenance therapy. **Results:** The median age of enrolled patients was 71.5 years (range, 63 to 82 years), and 16 patients (72.7%) were over 70 years of age. The overall response rate (ORR) was 77.3% (n = 17) and the complete remission (CR)/complete remission with incomplete recovery (CRi) rate was 63.6% (n = 14) after the first induction cycle. With a median follow-up of 12.4 months, eight patients (57.1%) relapsed, with a median time to relapse of 12.3 months. The median duration of response (DOR) was 11.9 months (95% CI, 6.4 to NA months), the median overall survival (OS) was 15 months (95% CI, 8.4 to 21.6 months), and the median progression-free survival (PFS) was 7.5 months (95% CI, 4.6 to 15.1 months). Common grade 3 or greater adverse events included febrile neutropenia (77.8%) and infection (63.6%), with pneumonia being the most common (10, 45.5%). There was one death (4.5%) within 30 days. **Conclusion:** The combination of PLD, LDAC, and G-CSF is well-tolerated and exhibits high rates of CR/CRi and low early mortality, providing an attractive treatment option for newly diagnosed elderly and unfit AML patients.

Keywords

older, unfit, acute myeloid leukemia, chemotherapy, liposomal doxorubicin

Received: August 22, 2024; Revised: November 1, 2024; Accepted: December 17, 2024.

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Trial registration: The trial was registered at chictr.org.cn (ChiCTR2100045069). Registered at 4 April 2021.

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Introduction

Acute myeloid leukemia (AML) is a group of diseases characterized by high molecular and clinical heterogeneity. The age-adjusted annual morbidity is 4.3 per 100,000, with a median age of onset of 68 years.[1] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) and intensive chemotherapy significantly improve the overall survival rate in younger patients, but not in elderly patients.[2]

There are limited treatment options for unfit elderly AML patients. Even after decades of development, the traditional "7 + 3" regimen (7 days of cytarabine combined with 3 days of anthracycline) remains to the backbone of intensive chemotherapy for AML. 7 days of cytarabine and 3 days of daunorubicin (DNR) is the most widely used "7 + 3" regimen, which can yield complete remission (CR) rates of 60%–80% in younger patients and 45%–60% in older patients (age $\geq$ 60 years).[3] However, its severe adverse events preclude a large proportion of elderly patients who have complex comorbidities.[4] Single hypomethylating agents (HMAs) therapy, while less toxic, has a CR/CRi rate of only 27.8% and a median overall survival (OS) of 9.6 months.[5] HMAs combined with venetoclax have increased the CR/CRi rate to 66.4% and the median OS to 14.9 months.[6] The well-tolerated and high response rates of this combination are increasingly confirmed by clinical trials, however, OS remains poor. Increased hematological toxicity and febrile neutropenia are common, and drug resistance is not unusual.[7] Targeted therapy can improve efficacy, but their high costs render them inaccessible for some patients, particularly in developing countries. It is necessary to develop new chemotherapy regimens that have less adverse effects, fair efficacy, and affordable costs for elderly unfit AML patients.

As one of the anthracyclines, doxorubicin (DOX) shares a very similar structural formula with DNR and has been the mainstay of various cancer therapies for a long time by inhibiting topoisomerase II and generating free radicals.[8] Although DNR is mainly chosen in the traditional "7 + 3" regimen for historical reasons, DOX is applied and shows comparable efficacy to DNR in leukmia.[9] Liposomes, as a drug carrier, exhibit outstanding properties in prolonging half-life, enhancing targeted uptake, and reducing side effects.[10] Pegylated liposomal doxorubicin (PLD) has been available in China and significantly prolongs blood circulation time, with the area under the curve (AUC) at least 60 times greater than that of DOX. This strongly increased the concentration in tumor tissues without increasing the drug dose.[8,9] PLD combined with other drugs have achieved fair results in the treatment of AML.[11,12] It provides comparative efficacy with reduced myelosuppression and cardiotoxicity compared to DOX,[13] making it more suitable for older AML patients. CPX-351 is a dual-drug liposomal encapsulation of cytarabine and DNR at a fixed 5:1 molar ratio. It has shown a survival advantage and fewer comorbidities for older patients and those with secondary AML compared to 7 + 3 regimen.[14-16] Unfortunately, CPX-351 is not yet been available in China. Low dose of cytarabine showed comparable anti-tumor efficacy and less toxicity.[17] PLD combined with subcutaneously injected low dose cytarabine may simulate the sustained and stable anti-leukemia effects of CPX-351. G-CSF priming has been found to enhancing G0 resting AML cells into the cell cycle, potentiating the cytotoxicity of the regimen against AML cells.[18] According to CAG (LDAC, aclarubicin and G-CSF) regimen,[19] the addition of G-CSF can enhance the efficacy of LDAC and PLD in treating AML.

Based on these data, we investigated combination therapy using PLD, LDAC, and G-CSF in newly diagnosed elderly unfit AML patients. With stable concentration and reduced toxicity, this chemotherapy regimen is expected to improve the overall response rate and increase tolerance in elderly AML patients.

Methods

Patients

This open-label, single center, single arm prospective trial enrolled inpatients between May 2021 and March 2024. The trial was registered on chictr.org.cn (ChiCTR2100045069) on 4 April, 2021. Patients aged 60 years or older with untreated AML, who were ineligible for intensive chemotherapy[20] and willing to participate, were enrolled. Patients with secondary AML were included. The exclusion criteria were as follows: 1. Patients with acute promyelocytic leukemia; 2. Patients with Eastern Cooperative Oncology Group (ECOG) performance status 4; 3. Prior therapy for AML or any previous use of cytarabine for any indication; 4. Severe cardiopulmonary and other important organ dysfunction, or intolerance as evaluated by researchers; 5. Patients with severe mental diseases who can't follow the treatment protocol; 6. Patients with other malignant tumors requiring treatment. Ethics committee approval was obtained and patients provided written informed consent. The study was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, and the Declaration of Helsinki.

Treatment

Patients with hyperleukocytosis were pretreated with hydroxyurea or leukapheresis. Tumor lysis syndrome prophylaxis (hydrating, alkalizing and microcirculation improvement) was initiated before chemotherapy. Pegylated liposomal doxorubicin (PLD) was administered by intravenous injection. A total dosing of 25 mg/m^2 was divided into doses on days1 (D1), 3 (D3), and 5 (D5), administered once a day. Low-dose cytarabine (LDAC) (15 mg/m^2) was administered by subcutaneous injection twice a day from D1 to D14. Granulocyte colony-stimulating factor (G-CSF) 150–300ug was started intravenously the day before chemotherapy and was withdrawn when the white blood cell (WBC) was above 20×10^9/L.

One cycle of induction, four cycles of consolidation and indefinite maintenance was planned, all consisting of PLD, LDAC, and

G-CSF. If the AML did not achieve CR/CRi after one cycle of induction, or if it relapsed during consolidation or maintenance, a switch to another chemotherapy regimen or try this combination regimen at most once. Each cycle lasts 28 days. If patients continued to be negative minimal residual disease (MRD) for two cycles, the maintenance interval could be extended to every two months. The MRD was tested by multiparameter flow cytometry. The next cycle of therapy was initiated only when the neutrophil count recovered to at least 0.5 $*10^9$/L and the platelet count recovered to at least $20*10^9$/L. Bone marrow assessments, including smear and MRD testing, were performed after each cycle. Efficacy was evaluated after every cycle. During induction, consolidation and maintenance chemotherapy, patients were hospitalized until hematological recovery. Blood counts test was followed up weekly after discharge.

Assessment of Response and Toxicities

Maximum toxicities were monitored and graded according to the World Health Organization (WHO) grading criteria for toxicities. Clinical responses were defined according to the International Working Group response criteria for AML.[21]

Outcomes

The primary endpoint was the overall response rate (ORR), comprising of the complete remission (CR), complete remission with incomplete recovery (CRi), and partial response (PR), measured after the first cycle of therapy. The secondary endpoint was overall survival (OS), progression-free survival (PFS), duration of response (DOR), MRD negative rate, and relapse rate. OS was measured from the start of chemotherapy until the date of death due to any cause or censored at the date of the last follow-up. PFS was measured from the date of chemotherapy until relapse or death from any cause, whichever occurred first. Censored was defined as patients who were alive and without disease relapse at the time of the last follow-up. DOR was defined as the time between the date of response and the date of disease relapse or death from any cause among responders, whichever occurred first.

Statistical Analyses

All baseline summary statistics and analyses were based on patient characteristics obtained before the initiation of chemotherapy. Time to event endpoints including OS, PFS and DOR, were estimated using the method of Kaplan-Meier. The Log-rank test was used for comparison between subgroups for OS and PFS. All analyses were done using R.

Results

Patient Clinical Characteristics:

Twenty-two patients were enrolled in this study. All patients had been newly diagnosed as AML and were unsuitable for intensive chemotherapy. The flowchart shown in Figure 1 consisted of one cycle of induction followed by four cycles of consolidation and maintenance. The majority were male (63.6%). Of the 22 patients, sixteen (72.7%) were over 70 years old, with a median age of 71.5 years (range, 63 to 82 years). Ten (45.5%) patients with a WBC greater than 20×10^9 /L at diagnosis received hydroxyurea, five of these patients underwent additional leukapheresis due to WBC levels exceeding 100×10^9/L. None of these patients were primed with G-CSF. The median bone marrow blast percentage at diagnosis was 56.5% (range, 22% to 91%). Only one patient developed secondary AML following Hodgkin's lymphoma, while the others had de novo AML. Most patients had an ECOG score of 2 to 3. Two patients were categorized as favorable risk, six (27.3%) as intermediate risk, and fourteen (63.6%) as poor risk according to ELN 2022.[22] The primary comorbidities impacting allo-HSCT[23] were diabetes (8, 36.4%), infection (7, 31.8%), cardiac diseases (6, 27.3%), renal dysfunction (4, 18.2%), and pulmonary dysfunction (2, 9.1%) (Table 1).

Efficacy:

At data cutoff, all patients had been enrolled at least 3 months prior to this analysis. Three patients (13.6%) remained on treatment, while 2 patients (9%) lost follow-up, and 17 patients (77.3%) died due to leukemia-related complications. The median total treatment cycles were 6 (1 to 10). After the first cycle of induction, CR was achieved in 41% of patients (n = 9), with 5 patients achieving CRi, 3 patients achieving PR and, and 5 patients showing not response (NR) (Figure 2A). All 5 patients who reached CRi achieved hematological improvement in hemoglobin and platelets. The ORR rate was 77.2% (n = 17) and the CR/CRi rate was 63.6% (n = 14). Among the patients achieving CR/CRi, nine (64.3%) also attained MRD negativity

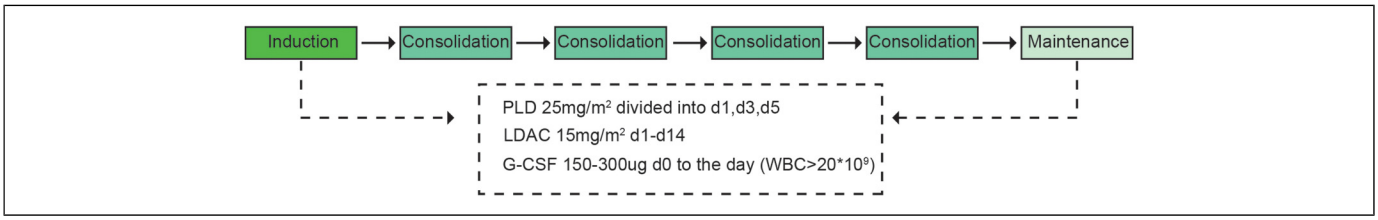

Figure 1. The flowchart. The PLD + LDAC + G-CSF regimen for newly diagnosed older and unfit AML patients consists of one induction cycle, four consolidation cycles, and subsequent maintenance. AML, acute myeloid leukemia; PLD, pegylated liposomal doxorubicin; LDAC, low-dose cytarabine; G-CSF, granulocyte colony-stimulating factor.

Table 1. Characteristics and Hematological Features of Newly Diagnosed Elderly Unfit AML Patients Receiving PLD + LDAC + G-CSF Regimen Therapy

Variable	Value
No. of patients (%)	22 (100)
Age, years (median, range)	71.5 (63-82)
Sex (male), (n, %)	14 (63.6)
White blood cell count $\times 10^9$ /L (median, range)	12.7 (1.4-239.7)
White blood count $\geq 20 \times 10^9$ /L (n, %)	10 (45.5)
White blood count $\geq 100 \times 10^9$ /L (n, %)	5 (22.7)
Hemoglobin level, g/dl (median, range)	7.6 (3.5-11.9)
Platelet count $\times 10^9$ /L (median, range)	45 (7-181)
Bone marrow blasts % (median, range)	56.5 (22-91)
Peripheral blasts % (median, range)	22.5 (0-99)
AML type (n, %)	
De novo	21 (95.5)
Secondary	1 (4.5)
ECOG (n, %)	
1	1 (4.5)
2	11 (50)
3	10 (45.5)
Somatic mutation* (n, %)	
DNMT3A	4 (18.2)
FLT3	3 (13.6)
RUNX1	3 (13.6)
WT1	3 (13.6)
NPM1	2 (9.1)
TP53	2 (9.1)
KRAS/NRAS	2 (9.1)
CEPBPA	2 (9.1)
BCOR	2 (9.1)
IDH1/IDH2	2 (9.1)
JAK2	2 (9.1)
Cytogenetic risk category (n, %)	
Favorable	0
Intermediate	10 (45.5)
Poor	12 (54.5)
ELN 2022 risk stratification (n, %)	
Favorable	2 (9.1)
Intermediate	6 (27.3)
Poor	14 (63.6)
Comorbidities (n, %)	
Diabetes	8 (36.4)
Infection	7 (31.8)
Cardiac diseases**	6 (27.3)
Renal dysfunction	4 (18.2)
Pulmonary dysfunction	2 (9.1)

*The mutant gene is only shown if it is present in at least two patients.
**Cardiac diseases include coronary artery disease, congestive heart failure, myocardial infarction and valvular disease (except mitral prolapse).

as determined by flow cytometry. The median time to first CR/CRi was 1.1 months (range, 0.8 to 1.7 months). Eight (57.1%) patients relapsed with a median time of 10.2 months (range, 3 to 18.6 months). Three patients relapsed during maintenance and 5 patients relapsed during consolidation. Among the responders after the first cycle, the median DOR was 11.9 months (95% CI, 6.4 to NA months) (Figure 2B). None of the patients underwent allo-HSCT. With a median follow-up of 12.4 months (range, 0.5 to 24.8 months), the OS was 15.1 months (95% CI, 8.4 to 21.6 months), and PFS was 7.5 months (95% CI, 4.6 to 17.5 months) (Figure 2C, D). Kaplan-Meier estimates indicated a 1-year OS of 53% and a 2-year OS of 15.7%. The estimated 1-year PFS was 35%. Patients who achieved CR/CRi had longer OS and PFS than patients who did not (supplementary Figure 1 A, B).

Safety

All patients were evaluable for safety. A 71-year-old patient died of septic shock 11 days after starting chemotherapy. She had multiple underlying diseases, an ECOG score of 3, and was classified in the poor risk group of ELN. None of the others patients died within 60 days of initial induction chemotherapy, and the 30-day and 60-day mortality were 4.5%. Among the 15 patients who achieved CR/CRi, two patients died during sustained remission of leukemia. One died from sever bacterial pneumonia after the fifth chemotherapy, while the other succumbed to COVID-19 during the pandemic after completing the sixth chemotherapy. The non-relapse mortality (NRM) was 14.3% (2/15). Consistent with expectations for chemotherapy in AML, hematologic adverse events (AEs) happened to every patient. The time required for platelet ($>20 \times 10^9$/L) recovery and neutrophil (0.5×10^9/L) recovery was assessed among patients who achieved CR/CRi after initial induction chemotherapy. The median time from the start of treatment to platelet recovery was 19.5 days, with all patients reaching this threshold by day 34. The median time from the start of treatment to neutrophil recovery was 20 days, with all patients reaching this threshold by day 28. (Figure 3A). AEs grade 3 were mainly febrile neutropenia and infection. The former was reported in 17 (77.8%) patients, while the latter was reported in 14 (63.6%) patients. Pneumonia (10, 45.5%) was the most common infection, followed by urinary tract infection (2, 9%) and bacteremia (4, 18.2%) (Figure 3B). The most frequent AEs grade < 3 included nausea (14, 63.6%) and hypokalemia (8, 36.4%). Two patients experienced transient cardiotoxicity with AEs of grade < 3 (Figure 3C). One patient carried rheumatic and coronary heart disease and accepted coronary stenting. Another patient had valvulopathy. All AEs were manageable without dose interruption.

Discussion

The elderly are the primary victims of AML, but their prognosis is significantly worse compared to younger patients. Elderly individuals often present with reduced performance status, increased comorbidities, and higher genetic risk stratification, which limits the ability of some elderly AML patients to undergo intensive chemotherapy and subsequent allo-HSCT.[24,25] Current treatment choice for elderly patients with unfit AML are limited and unsatisfactory. There is a need for treatments that ensure longer survival, lower toxicity and affordability, so the exploration of therapies for senile AML must continue. Inspired by CPX351 and CAG regimen,

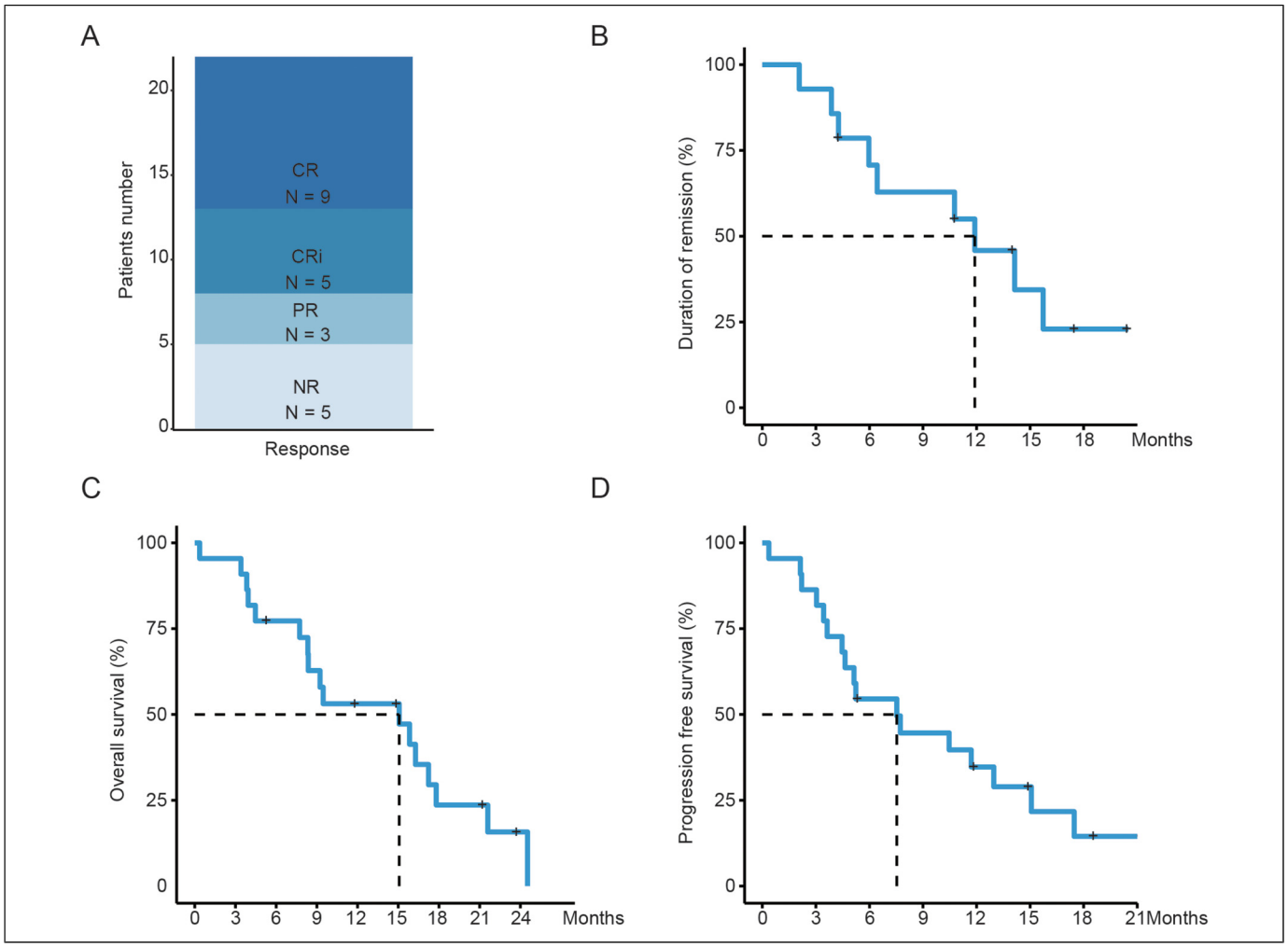

Figure 2. Efficacy of PLD + LDAC + G-CSF regimen in newly diagnosed older and unfit AML patients. (A) Response to treatment. (B) Duration of remission (DOR) for patients who had CR/CRi. (C) Overall survival (OS) of all patients; (D) Progression free survival (PFS) of all patients. CR, complete remission; CRi, complete remission with incomplete recovery; PR, partial response; NR, not response. OS, DOR, and PFS were analyzed using Kaplan-Meier methodology.

we developed a combination of PLD + LDAC + G-CSF for newly diagnosed elderly patients with unfit AML. This combination is reported for the first time, and its efficacy and safety have been demonstrated.

Unfit older AML patients are rarely recommended for allo-HSCT due to the challenges of tolerating intensive chemotherapy prior to transplantation. A low-intensity regimen combined with subsequent allo-HSCT is under exploration and shows fair result,[26] but elderly AML patients are less likely to choose this regimen for a variety of reasons, especially in developing countries where suitable donors are less available and costs are more burdensome.[27] In the targeted therapy combined with HMAs, the CR/CRi rate of ivosidenib for IDH1 mutatation, enasidenib for IDH2 mutation, and gilteritinib for FLT3 mutatation are 47.2%,[28] 57%[29] and 58.1%,[30] respectively. But additional targeted therapy is not affordable for all patients. CPX351 has a CR/CRi rate of 55.2% and a median OS of 9.56 months.[14,15] Venetoclax combined with HMAs/LDAC in elderly participants has a CR/CRi rate ranging from 61% to 66.4% and a median OS of 12.3 to 14.9 months.[31,32] Our regimen combination shows excellent efficacy, with a CR/CRi rate of 63.6% and an OS of 15 months, which is comparable to venetoclax + HMAs/LDAC and CPX351. The mechanisms of venetoclax, cytarabine, and anthracycline differ, and each drug combination may offer advantages for specific AML types or leukemia cells. Our regimen may prove effective when resistance to venetoclax + HMAs/LDAC develops. CPX351 is more commonly used for AML with myelodysplasia-related changes and secondary AML.[14-16] Our regimen mimics CPX351, so whether our regimen possesses this feature warrants further investigation.

Tolerance and safety are the main concerns for unfit patients. With "7 + 3" intensive chemotherapy, the early mortality rate for the elderly (> 70y) can reach as high as 26%.[33] Single agent HMAs or LDAC reduce early mortality to less than 5% to 10% by sacrificing response rate. Recent report of CPX351 and venetoclax-based regimens both show a 30-day mortality around 6%.[15,32] In our study, the 30-day

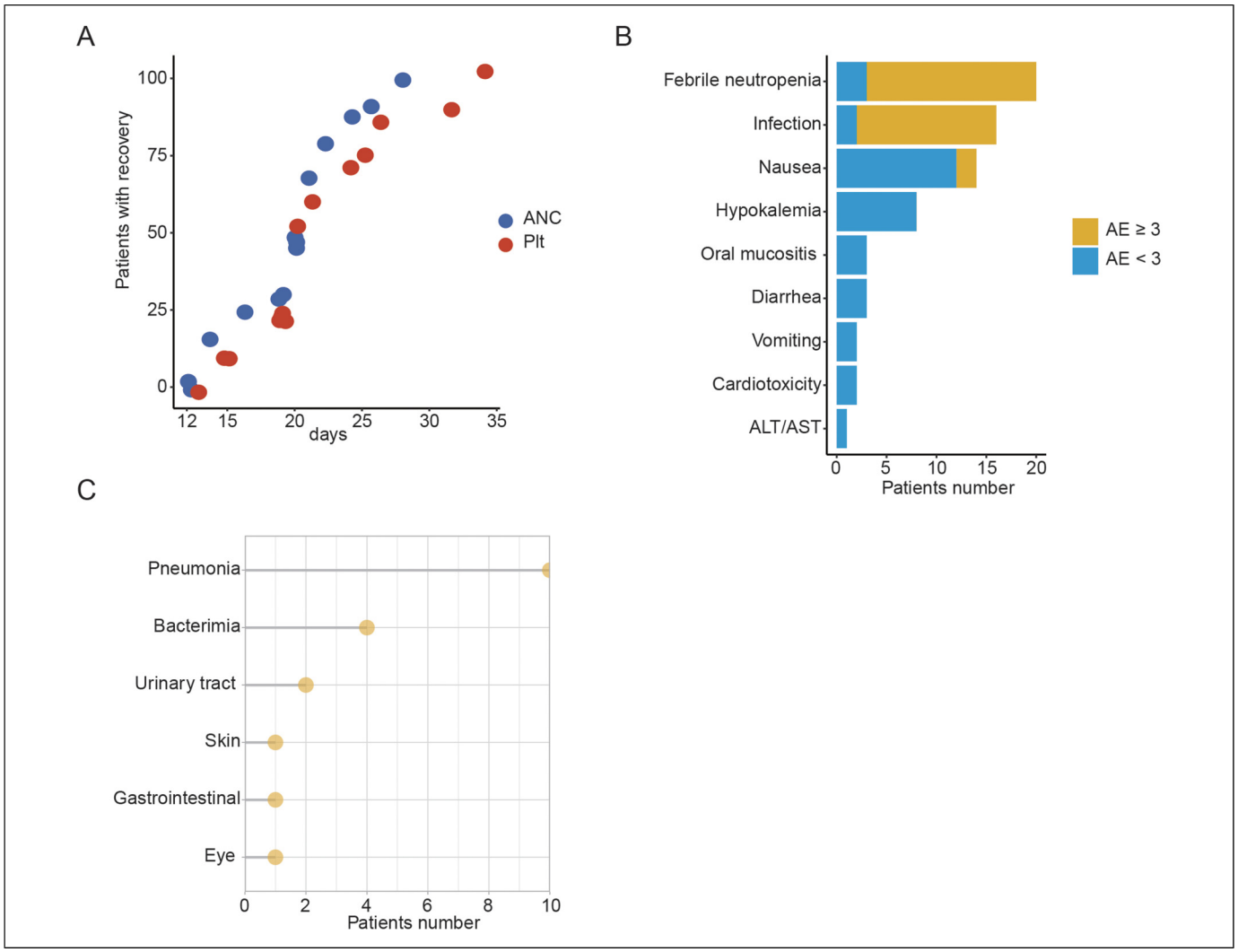

Figure 3. Summary of hematological recovery and treatment aes. (A) Time to Platelet and Neutrophil Recovery in Patients with CR/CRi. The graph shows the percentage of patients with recovery of platelets (red; platelets ≥ 20,000/μL) and neutrophils (blue; ANC ≥ 500/μL) over time. ANC, absolute neutrophil count; CR, complete remission; CRi, CR with incomplete blood count recovery. (B) Reported treatment associated AEs. The number of patients with grade < 3 (blue) and grade 3 (yellow) are shown for all adverse events that occurred. AEs, adverse events. (C) Infections in patients.

mortality was 4.5%. The small cohort may lead to an underestimation of mortality. A Longer time to achieve hematological recovery after chemotherapy may increase the risk of infection and bleeding, potentially delaying the next cycle of chemotherapy. The recovery of neutrophils and platelets in our study was surprisingly rapid, compared to about 30 days reported by most other studies.[14,32] Hematological toxicity in our study, mainly febrile neutropenia, is lower than that reported for CPX351 (91%),[14] but higher than that observed in venetoclax plus LDAC (42%)[32] or HMAs (42%).[7] Febrile neutropenia or infection may be more easily controlled when neutrophil recovered. Gastrointestinal reactions such as nausea, vomiting and diarrhea were less severe than those reported for venetoclax combined with LDAC. Cardiotoxicity with AEs grade < 3 was observed in 2 patients who had pre-existing cardiac disease. These mild AEs may may be attributed to liposomal doxorubicin[8] and a low dose of cytarabine.[17]

Given the high rate of relapse, particularly in patients without allo-HSCT, maintenance therapy is essential. However, the specific therapies and duration for AML maintenance have remained unclear. Current maintenance primarily involves continued cytotoxic chemotherapy, HMAs, immunotherapy, and targeted therapy.[34] Clinical trial data on maintenance is inconsistent. Some studies indicated that maintenance showed no difference in relapse or OS compared to observation,[35] while others suggested that maintenance improved disease-free survival (DFS) but not OS.[36] Oral azacitidine used as maintenance demonstrated survival benefits and received FDA approval.[37] However, it is not universally adopted and still requires clinical experience. In this study, considering good tolerance and efficacy, we continued with the

same chemotherapy regimen used for induction and consolidation. We extended the chemotherapy interval to minimize toxicity. Regardless of the chemotherapy used, developing drug resistance with repeated treatments is inevitable. The impact of using the same chemotherapy regimen on the likelihood of drug resistance during maintenance is not well studied. Can alternating drugs with different mechanisms enhance OS? This question regarding maintenance therapy warrants further investigation.

The limitations of our study are mainly reflected in the small sample size and the fact that it is a single-arm, single-center clinical research. Therefore, future studies need to expand the sample size and design more rigorous research to validate the efficacy and safety of this regimen. Nevertheless, our study protocol demonstrates a high rate of induced remission and good tolerance. Furthermore, the drug is readily available and inexpensive, providing a new treatment option for elderly patients with unfit AML.

Conclusions

Our study demonstrates fair efficacy and tolerance of PLD + LDAC + G-CSF combination.

The high rates of CR/CRi and reduced toxicity position our regimen as a promising option for elderly AML patients and those unfit for intensive chemotherapy, particularly in developing countries where treatment options are limited. Concurrently, larger-scale cohorts and multi-center studies are necessary to further validate these findings.

Acknowledgements

None.

Author Contributions

Shifeng Lou and Kang Zhou designed the study, Bingqing Luo and Xiaoyan Tan organized the data, and wrote the manuscript. Bingqing Luo collected the data and conducted the statistical analysis. Yanfang Zhang, Xiao Hu, Hanqing zeng and Hongbo Xiao treated the patients and provided patients' information. All authors critically reviewed and approved the manuscript.

Data Availability Statement

The datasets analyzed during the current study are available from the corresponding author on reasonable requests.

Declaration of Conflicting Interest

None of the authors have any conflict of interest to disclose.

Ethics Approval and Consent to Participate

The study was approved by the Second Affiliated Hospital, Chongqing Medical University (Ethical approval number: CQMU-2021-009; Approval Date: 2021.2.9). The procedures followed were in accordance with the Declaration of Helsinki. Written informed consent for participation in this clinical trial is required from all study participants.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Tracked Changes or Comments Where the Poster's Name is Listed

None.

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Supplemental Material

Supplemental material for this article is available online.

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