Outcome analysis of acute myeloid leukemia patients treated with high dose daunorubicin

Roya Dolatkhah1, Effat Irani Jam2, Alireza Nikanfar3, Ali Esfahani3, Sayed Hadi Chavooshi2, Babak Nejati2, Zohreh Sanaat4,*

ABSTRACT

Abstract: Acute Myeloid Leukemia (AML) is a malignant hematopoietic disease caused by the presence of a malignant clone in the bone marrow. The classic AML treatment includes a combination of an Anthracycline and Cytarabine. This study aimed to evaluate the effect of high doses of Daunorubicin on patients’ outcome. Methods: During the study period, 16 AML patients received induction therapy with Cytarabine (100 mg/m²/d) for 7 days and Daunorubicin (90 mg/m²/d) for 3 days. Outcome analysis was performed to evaluate the overall survival (OS) and disease-free survival (DFS) during 2 years of study. Results: The mean age of patients was 38 ± 12.38 years, with the age range between 16 and 54 years old. Seven patients (43.8%) were females, and 9 cases (56.3%) were males. OS was 81.3%, with a mean of 396.88 days. (95% CI: 306.99-486.77). DFS was 83.3%, with a mean of 383.57 days (95% CI: 299.88-467.26). The log-rank test showed a significant difference in DFS of AML sub-types, as M1 subtypes had lower DFS (P log-rank= 0.013). Although M1 subtypes had a lower OS, there was no significant difference in OS between subgroups (P log-rank= 0.067). Conclusion: Although disease-free survival was improved by increasing the dose of daunorubicin, there was no difference in the overall survival between the AML subgroups and sexes.

Key words: Acute Myeloid Leukemia, Induced Therapy, Disease-Free Survival, Overall Survival, Cytarabine, Daunorubicin

INTRODUCTION

Acute Myeloid Leukemia (AML) is a malignant hematopoietic tumor of the bone marrow myeloid cells1–3, which results in the aggregation of malignant cells in the bone marrow and the onset of anemia, neutropenia, thrombocytopenia1–8. The incidence of AML is more common in men, and the ratio of incidence in men to women is 3 to 2. The incidence of AML increases with aging9–12. Several etiologies are associated with AML incidence, including dysplastic diseases, congenital diseases (Down syndrome, Fanconi anemia), and environmental exposures (ionizing radiation, chemical exposures, and history of chemotherapy)13–15. In the absence of treatment, the median survival of patients is about 11 to 20 weeks16. AML treatment includes induction therapy (Remission Induction) and Post Remission Induction. The aim of Remission Induction is to achieve a complete response to treatment (Complete Remission). Despite recent improvements, the AML cure rate increased from 20% in the 1960s — 1980s, to 40-70% in 2000. AML standard treatment includes an Anthracycline and Cytarabine combination17.

The most widely used AML induction chemotherapy regimen is Cytarabine as a continuous infusion of 100-200 mg/m² for 7 days and intravenous Anthracycline for 3 days. Different dosages have been performed using Daunorubicin (30 mg/m²/d to 90 mg/m²/d) in other studies. This study aimed to determine the overall survival and disease-free survival in AML patient treated with 90 mg/m²/day of Daunorubicin.

MATERIALS - METHODS

This cross-sectional study was conducted between December 2015 to September 2017 in the Department of Hematology and Oncology, Tabriz University of Medical Sciences. This study has been approved as a confirmed research proposal (94/13) and obtaining the permission of the Ethics Committee of Tabriz University of Medical Sciences (TBZMED.REC.C1394.793). Ethical consent forms were obtained from all patients.

Inclusion criteria

All patients aged 15-60 years with newly diagnosed AML and other than AML (M3), based on morphological and flow cytometric criteria, and patients with...
Biomedical Research and Therapy, 6(9):3347-3351

Exclusion criteria

Patients during pregnancy and breastfeeding, or having malignancies and secondary or previously treated for AML, and patients with a cardiac ejection fraction of less than 50% were excluded.

After confirmation of the diagnosis of AML according to WHO diagnostic criteria (presence of more than 20% of myeloblasts in bone marrow), patients were treated with an induction regimen of 7 + 3. Morphological evaluation of cells, immune-histological staining, flow cytometric characteristics, and cytogenetic analysis for patients were performed.

Patients were treated with Cytarabine (Ebewe, Austria) 100 mg/m² as a 24-hour intravenous infusion for 7 days, and Daunorubicin 90 mg/m² (Pfizer, Germany) was infused intravenously for three days.

At the 30th day after treatment started, patients were evaluated for response to treatment by bone marrow aspiration.

In the case of complete remission (19), which included neutrophil count over 1000, platelet count above 100,000, absence of premature cells in peripheral blood and less than 5% in bone marrow, and absence of Auerrod, patients were treated with Cytarabine (100 mg/m²) as infusion during 24-hour for 5 days, and 45 mg/m² of Daunorubicin as intravenous infusion for two days. This treatment was repeated with an interval of one month, and patients underwent monthly blood tests until relapse or death due to non-AML.

Statistical analysis

Prognostic outcomes were assessed as overall survival (OS) and disease-free survival (DFS). Overall survival was determined at the time of diagnosis and the date of death or the last follow-up. DFS was evaluated at the time interval between the diagnosis date and the date of the first relapse or the last follow-up.

The survival analysis was performed using the Kaplan-Meier method and the log-rank test for evaluating the differences between mentioned factors. Data analysis was performed by SPSS software version 21.

RESULTS

Sixteen patients were recruited in this study, including 7 (43.8%) females and 9 (56.2%) males. The patients were between 16-54 years old, and their mean age was 38 ± 12.38 years. The most common detected subtype was AML, M2 (n=9, 56.25%). Table 1 shows the frequency of AML different subtypes (Table 1).

The median white blood cell count was 2125.0/cm³ (800 to 83480), with mean hemoglobin levels of 5.88 ± 2.66 g/dl, and the median platelet count was 29500.0/mm³ (5000 to 42000).

In 13 patients (81.3%), fever was reported, and mucositis was detected in 10 patients (62.5 %). The highest and lowest neutropenic periods in patients were 8 days and 26 days, respectively. The median duration of neutropenia was 23 days. The maximum and minimum days for antibiotic treatment were 8 days and 26 days, respectively, and the median duration of antibiotic therapy was 8 days. From 16 AML patients, only one patient had evidence of cardiac function reduction.

The mean follow-up time was 216.44 ± 178.08 days in 16 AML patients. The overall survival was 81.3%, with the mean OS of 396.88 days (95% CI: 306.261-486.765). The highest overall survival was observed for M2 sub-type, but there was no significant difference in prognosis between different AML subtypes (P Log-rank = 0.0 67). Although male patients had lower OS than females (77.8% vs. 85.7%), this difference was not significant (P Log-rank=0.640) (Figure 1).

The disease-free survival (DFS) was 83.3%, with a mean of 383.57 days (95% CI: 299.88 – 467.26). None of the M2 sub-types had relapsed during the study period, and so there was a significant difference in DFS between AML sub-types (P Log-rank=0.013). From each of the male and female AML cases, one patient had relapsed (P Log-rank=0.728) (Figure 2).

DISCUSSION

We followed 16 AML patients in two years to evaluate the prognostic effect of treatment with 90 mg/m²/day of Daunorubicin. The most common detected subtype was AML, M2 (n=9, 56.25%), and there was a significant difference of DFS between different subtypes, while none of the M2 sub-types had relapsed.

Recently Lee et al. (2016) showed the effectiveness of increasing Daunorubicin doses to 90 mg/m²/day compared to 45 mg/m²/day dosage, in the form of 7+3 protocol in patients younger than 60 years.

The overall remission rate was 70.6% vs. 57.33% (P<0.001), and the overall survival rate was 23.7 months, compared to 15.7 months (P=0.005) 18. In another study, the complete remission rate was 82.5%.
Table 1: Frequency of different AML subtypes

| AML Subtype | Frequency | Percent  |
|-------------|-----------|----------|
| M0          | 1         | 6.25%    |
| M1          | 3         | 18.75%   |
| M2          | 9         | 56.25%   |
| M4          | 3         | 18.75%   |
| M5          | -         | -        |

Figure 1: Overall Survival Function in 16 Patients with AML. A. In Males and Females, B. In Different Subtypes.

Figure 2: Diseases Free Survival Function in 16 Patients with AML. A. In Males and Females, B. In Different Subtypes.
CONFLICT OF INTEREST

None of the authors of this article have conflicting interests.

ACKNOWLEDGMENTS

The authors would like to thank all the patients participating in this research and the Hematology and Oncology Research Center of Tabriz University of Medical Sciences to support this proposal (Scheme: 94/13), approved by the Ethics Committee of the Tabriz University of Medical Sciences (TBZMED. REC.1394.793). The present study is a thesis of Dr. Efat Irani Jam, MD, in the Faculty of Medicine, Tabriz University of Medical Sciences (Thesis no: 94/5-10/4).

REFERENCES

1. Ley TJ, Miller C, Ding L, Raphael BJ, Mungall AJ, Robertson A. Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. The New England journal of medicine. 2013 May 30;368(22):2059–74. PMID: 23634996. Available from: https://doi.org/10.1056/NEJMoa1301689.
2. Döhner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. The New England journal of medicine. 2015;373(12):1136–52. PMID: 26376137. Available from: https://doi.org/10.1056/NEJMra1406184.
3. Estey E. Acute myeloid leukemia: 2013 update on risk-stratification and management. American journal of hematology. 2013;88(4):318–27. PMID: 23526416. Available from: https://doi.org/10.1002/ajh.23404.
4. Estey E, Döhner H. Acute myeloid leukaemia. Lancet. 2006 Nov 25;368(9550):1894–907. PMID: 17126723. Available from: https://doi.org/10.1016/S0140-6736(06)67808-8.
5. O'Donnell MR, Abboud CN, Altman J, Appelbaum FR, Arber DA, Attar E. NCCN Clinical Practice Guidelines Acute myeloid leukemia. Journal of the National Comprehensive Cancer Network : JNCCN. 2012 Aug;10(8):984–1021. PMID: 22878824. Available from: https://doi.org/10.6004/jnccn.2012.0103.
6. Rubnitz JE, Gibson B, Smith FO. Acute myeloid leukemia. Hematology/oncology clinics of North America. 2010 Feb;24(1):35–63. PMID: 20113895. Available from: https://doi.org/10.1016/j.hoc.2009.11.008.
7. Stone RM, O'Donnell MR, Sekeres MA. Acute myeloid leukemia. Hematology American Society of Hematology Education Program. 2004.p. 98–117. PMID: 15561679.
8. Su L, Zhu X, Gao S, Li W, Liu X, Tan Y. High-dose versus standard-dose daunorubicin in induction therapy for young patients with de novo acute myeloid leukemia: a meta-analysis of randomised trials. Journal of chemotherapy. 2016 Apr;28(2):123–8. PMID: 27104964. Available from: https://doi.org/10.1080/1120009X.2015.1133011.
9. Creutzig U, Dworzak MN, Bochennek K, Faber J, Flotho C, Graf N. First experience of the AML-Berlin-Frankfurt-Munster group in pediatric patients with standard-risk acute promyelocytic leukemia treated with arsenic trioxide and all-trans retinoic acid. . Pediatric blood & cancer. 2017;64(8). PMID: 28111878. Available from: https://doi.org/10.1002/pbc.26461.
10. Luskin MR, Lee JW, Fernandez HF, Abdel-Wahab O, Bennett JM, Ketterling RP. Benefit of high-dose daunorubicin in AML induction extends across cytogenetic and molecular groups. Blood. 2016;127(12):1551–8. PMID: 26755712. Available from: https://doi.org/10.1182/blood-2015-07-657403.
11. Vaezi M, Bahar B, Mousavi A, Yaghmai M, Kasaean A, Souri M. Comparison of 60 and 80 mg/m(2) of daunorubicin in induction therapy of acute myeloid leukaemia. Hematological oncology. 2017;35(1):101–5. PMID: 26362260. Available from: https://doi.org/10.1002/hon.2236.

12. Wingo PA, Cardinez CJ, Landis SH, Greenlee RT, Ries LA, Anderson RN. Long-term trends in cancer mortality in the United States, 1930-1998. Cancer. 2003;97(12):3133–275. PMID: 12784323. Available from: https://doi.org/10.1002/cncr.11380.

13. Aquino VM. Acute myelogenous leukemia. Current problems in pediatric and adolescent health care. 2002;32(2):50–8. PMID: 11951090. Available from: https://doi.org/10.1067/mps.2002.121791.

14. Deschler B, Lubbert M. Acute myeloid leukemia: epidemiology and etiology. Cancer. 2006;107(9):2099–107. PMID: 17019734. Available from: https://doi.org/10.1002/cncr.22233.

15. Pogoda JM, Preston-Martin S. Smoking and risk of acute myeloid leukemia in adults. Cancer causes & control. 2006 Apr;17(3):351–2. PMID: 16489543. Available from: https://doi.org/10.1007/s10552-005-0581-2.

16. Sekeres MA, Stone RM, Zahrried D, Neuberg D, Morrison V, and DJDA. Decision-making and quality of life in older adults with acute myeloid leukemia or advanced myelodysplastic syndrome. Leukemia. 2004 Apr;18(4):809–16. PMID: 14762444. Available from: https://doi.org/10.1038/sj.leu.2403289.

17. Tallman MS, Gilliland DG, Rowe JM. Drug therapy for acute myeloid leukemia. Blood. 2005;106(4):1154–63. PMID: 15870183. Available from: https://doi.org/10.1182/blood-2005-01-0178.

18. Lee JH, Joo YD, Kim H, Bae SH, Kim MK, Zang DY. A randomized trial comparing standard versus high-dose daunorubicin induction in patients with acute myeloid leukemia. Blood. 2011 Oct 6;118(14):3832–41. PMID: 21828126. Available from: https://doi.org/10.1182/blood-2011-06-361410.

19. Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE. Age and acute myeloid leukemia. Blood. 2006 May 1;107(9):3481–5. PMID: 16455952. Available from: https://doi.org/10.1182/blood-2005-09-3724.

20. Lowenberg B, Ossenkoppele GJ, Putten WV, Schouten HC, Graux C, Ferrant A. High-dose daunorubicin in older patients with acute myeloid leukemia. The New England journal of medicine. 2009;361(13):1235–48. PMID: 19776405. Available from: https://doi.org/10.1056/NEJMoa0901409.