A clinical report on high-dose cytarabine therapy for children with acute myeloid leukemia

ZILIANG WU, ZELIN WU, YAWEI ZOU, JINGMING GUAN, SHANGZHI WU and DEHUI CHEN

Department of Pediatrics, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong 510120, P.R. China

Received February 26, 2022; Accepted June 7, 2022

DOI: 10.3892/mco.2022.2589

Abstract. Despite improvement in the long-term survival rate following pediatric acute myeloid leukemia (AML), the rate remains low, even with optimal treatment. The present study reports the long-term outcome of a small patient group treated with a single drug, high-dose chemotherapy (HDCT) with cytarabine, including consolidation and maintenance therapy. RT-PCR was conducted to assess 43 fusion genes, and after treatment, all cases have been followed up for 20 years (June 2002-December 2020). With an 80% 5-year survival rate, the results of this study highlight the possibility that pediatric AML can be reasonably effectively treated with relatively simple chemotherapy when necessary. HDCT is clinically safe, effective and relatively inexpensive. We propose that in the context of limited resources, HDCT should be considered as an alternative therapy for pediatric AML.

Introduction

Acute myeloid leukemia (AML) is a disorder of hematopoietic stem cells that occurs due to genetic alterations characterized by overproduction of neoplastic clonal myeloid stem cells (1). Over the past 28 years, the global incidence of AML has increased by 87.3% from $63.84x10^3$ cases in 1990 to $119.57x10^3$ cases in 2017 (2), with a mortality rate of ~3.2% (3). Despite advances in treatment, therapeutic options for AML are limited to high-dose cytotoxic chemotherapy. The 5-year survival rate of pediatric acute myeloid leukemia (AML) with chemotherapy alone remains low (4). In addition, there is the problem of limited resources for the frequently complex and costly associated treatments. Over the past 20 years, high-dose chemotherapy (HDCT) with cytarabine has been administered to pediatric patients with AML in the First Affiliated Hospital of Guangzhou Medical University, and the efficacy with respect to 5-year and longer overall survival (OS) and event-free survival (EFS) in children with AML has been assessed. The introduction of this treatment regimen was based on the study by Herzig *et al* (5), where high-dose Ara-C was applied in the maximally tolerated regimen of 3 g/m^2 every 12 h for 6 days for refractory leukemia and 70% of these patients responded, with 51% complete remissions. The present study aimed to investigate the efficacy of the regimen for pediatric patients with AML, providing an actionable and effective option for physicians as well as patients.

Patients and methods

Patients. A total of 15 patients [9 male and 6 female; age range, 1.2 to 12 years (median 6.7 years)], who had been diagnosed with AML in the First Affiliated Hospital of Guangzhou Medical University (Guangzhou, China) were enrolled and administered HDCT with cytarabine between June 2002 and May 2015 (Table I) after obtaining informed consent from their parent's or legal guardians. Patients diagnosed with AML-M3, AML with Down's syndrome or secondary AML were excluded. All patients presented with a high initial white blood cell count of $\geq 100x10^9/l$ (normal count range, $4.5\text{-}11.0x10^9/l$) and symptoms of bone pain, fever, localized swelling or weakness. Patients who received complete HDCT with a dose of 108 g/m^2 were included in the final analysis. The trial was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University and conducted in compliance with the Declaration of Helsinki.

Treatment. Following standard induction therapy using a DAE regimen [3 days of daunorubicin (40 mg/m^2/day) for 3 consecutive days, cytarabine (100 mg/m^2/day) for 7 consecutive days and etoposide (0.05-0.075/m^2/day) for 10 consecutive days] (6), consolidation therapy consisted of Ara-C (3 g/m^2 twice daily) from days 1 to 6 (total cumulative dose, 36 g/m^2), followed by consolidation chemotherapy with Ara-C (3 g/m^2, every 12 h) on days 1, 3 and 5 of 3 consecutive weeks (total cumulative dose, 108 g/m^2.) After discharge from the hospital, the patients regularly received maintenance treatment for 3 years, with the dosage and intervals (up to every 3-6 months in the first year and every 6-12 months in the second and third years) based upon the condition of the patient and identification of remaining

Correspondence to: Professor Ziliang Wu, Department of Pediatrics, First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang West Road, Yuexiu, Guangzhou, Guangdong 510120, P.R. China
E-mail: wuziliangguang@126.com

Key words: children, acute myeloid leukemia, high-dose Ara-C, event-free survival, pediatric

leukemia cells (minimal residual disease). Re-examination was performed at 1 year after the start of treatment.

Reverse transcription-polymerase chain reaction (RT-PCR). Since fusion genes might provide targets for the treatment and monitoring of myeloid leukemia, and some fusion genes such as MLL/AF4 and AML1/MTG8 frequently appear in AML (7,8), RT-PCR was performed in this study and the presence of abnormal fusion genes was identified. RNA was extracted from tissues using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) and reverse transcribed to cDNA. The cDNA was subjected to amplification and qPCR to detect the 43 fusion genes that were identifiable in leukemia at the time of the study, which was performed by Kindstar Globalgene Technology Inc.

At the time of writing this study, all cases have been followed up for 20 years (June 2002-December 2020).

Survival analysis. The survival data were plotted on a Kaplan-Meier curve. EFS time was defined as the time from diagnosis to the last follow-up visit without event. OS time was defined as the time from the diagnosis to the last follow-up visit or the time of death from any cause. Events included tumor recurrence (n=2), development of a secondary malignancy (n=1), irreversible complications of chemotherapy and death.

Results

The majority of cases were negative for the 43 fusion genes identifiable in leukemia at the time of the study, with only two cases positive for the fusion protein AML1/ETO.

The 5-year OS and EFS rates of the 15 cases were each 80±10% (Fig. 1). There were 2 cases of recurrence (13.3%) and 1 case of chemotherapy-related death (6.7%) (Table I).

All cases had varying degrees of myelosuppression after HDCT, as expected. Approximately one-half had fever, myalgia and bone pain, and occasionally chest pain, maculopapular rash, conjunctivitis and other symptoms 6-12 h after administration. The general condition of the patients was satisfactory, although antibiotics were not effective for patients with a high fever (n=2), suggesting they had the rare post-cytarabine syndrome, which is characterized by a fever, malaise, myalgia, arthralgia and/or a rash (9). In this case, corticosteroids were used for prevention and treatment.

Discussion

The prognosis of pediatric AML has been improving over the years; however, in most collaborative groups, the 5-year OS rate after chemotherapy alone remains at ~75% (10). Schweitzer *et al* (11) found that treatment using the AML-Berlin-Frankfurt-Münster (BFM) 2004 protocol (not with chemotherapy alone) yielded a 5-year OS rate as high as 70% in patients with acute megakaryoblastic leukemia, where patients received a randomized induction therapy of Ara-C, liposomal daunorubicin (L-DNR) and etoposide. Similarly, Rubnitz *et al* (12) reported 3-year OS and EFS rates of 75 and 66%, respectively, in children aged 0 to 9 years who underwent AML-02 treatment [high-dose cytarabine (3 g/m^2 every 12 h on days 1, 3 and 5) or low-dose

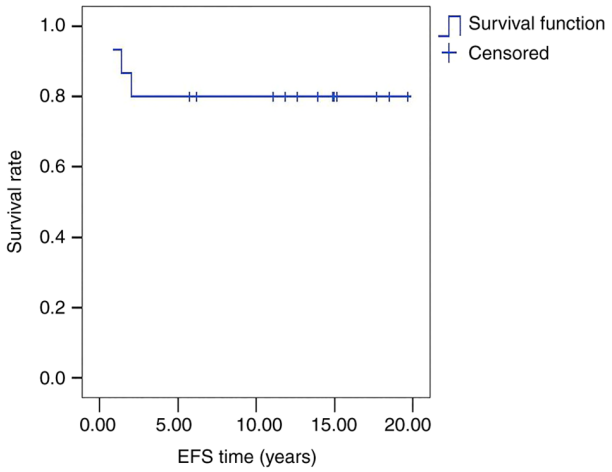

Figure 1. Overall survival and EFS in 15 children with acute myeloid leukemia after HDCT. There were 2 cases of recurrence (13.3%) and 1 case of chemotherapy-related death (6.7%). All patients received complete HDCT with a 20-year follow-up. EFS, event-free survival; HDCT, high-dose chemotherapy.

cytarabine (100 mg/m^2 every 12 h on days 1-10) plus daunorubicin (50 mg/m^2 on days 2, 4, and 6) and etoposide (100 mg/m^2 on days 2-6)]. The primary cause of treatment failure in AML is the high risk of recurrence, and thus increasing the intensity of consolidation treatment after remission might be beneficial (13). Notably, the application of high-dose Ara-C in the consolidation phase has resulted in better outcomes (14).

In the present study, HDCT therapy was improved upon by increasing the dosage of Ara-C and combining consolidation and maintenance therapy. In 2002, treatment with Ara-C was started for pediatric AML, using standard induction therapy followed by HDCT as aforementioned. The cumulative dose of 108 g/m^2 cytarabine is 3 times the maximum dosage suggested by Herzig *et al* (1983) (5). A complete regimen of HDCT achieved 5-year EFS and OS rates of 80%.

In recent years, the application of high-dose cytarabine in the consolidation phase has resulted in better AML treatment outcomes worldwide. The treatment regimens used by the various collaborative groups are basically similar, and these have been found to achieve a remission rate of ~90% (15).

Although only a small number of patients were enrolled in the present study, the follow-up time was long at up to 20 years. This allowed a long-term assessment of efficacy, proving the durability of the curative effect. One patient (male, 4 years old, M2 type) was admitted to the hospital and received only one course of treatment, in January 2001. The patient was withdrawn from the therapy in the early intensive phase for economic reasons and therefore was excluded from the analysis.

AML is still known as a threat to humans, and in China, investigators keep exploring better therapeutic approaches for the disorder. In recent years, some significant advances have occurred in the treatment for AML, such as the addition of gemtuzumab ozogamicin (GO) or bortezomib to traditional chemotherapy, which have improved the prognosis (EFS, 48% with GO vs. 29% without; OS, 63% with GO vs. 53%

Table I. Testing for the 43 fusion genes in 15 patients with acute myeloid leukemia.

Case	Sex	Admission date	Onsetage, years	Classification[a]	Immunophenotype	Chromosome analysis	Fusion gene	High-dose Ara-C, g/m^2	Outcome at 2022 (>5 years)
1	Male	June 2002	8	M2	Juvenile cells mainly expressed CD13 73.24%, HLA-DR 64.76%, HLA-DR/CD13 59.40%, CD19/CD13 0.33%, CD19/CD10 0.2%, CD22 0.12%	Unchecked	Negative for AML1/ETO	108	Survival
2	Male	February 2003	5	M2	CD19 42.92%, CD13 91.67%, HLA-DR 80.87%, HLA-DR/CD13 77.63%, CD33/CD13 23.99%, CD15/CD14 0.24%, CD19/CD13 76.32%	Unchecked	Negative for AML1/ETO	108	Survival
3	Male	May 2003	12	M4EO	Juvenile cells mainly expressed CD13 99.38%, HLA-DR 56.04%, HLA-DR/CD13 53.6%, CD14 43.07%, CD34 11.28%, CD34/CD14 0.39%, MPO 47.63%, MPO/CD34 21.85%	Negative	Negative for AML1/ETO	108	Survival
4	Female	November 2005	3	M1	CD7 71%, HLA-DR 40.21%, CD13 81.22%, MPO/CD13 59.22%	Unchecked	Negative for BCR-ABL, and AML1/ETO	108	Survival
5	Male	January 2006	10	M2	Juvenile cells mainly expressed CD7 51.36%, HLA-DR/CD13 25.71%, HLA-DR 56.53%, CD13 87.76%	Unchecked	Negative for BCR-ABL, and AML1/ETO	108	Survival
6	Male	February 2006	6	M2	Juvenile cells mainly expressed CD13 91.1%, CD117 4.78%, HLA-DR/CD15 75.23%, MPO 7.8%	Negative	Positive for AML1/ETO (>60%)	108	Survival
7	Male	February 2007	7	M2	Juvenile cells (65.57% of karyocytes) mainly expressed CD7 91.1%, CD33 4.78%, HLA-DR/CD7 75.23%, CD33/CD13 0.98%	Negative	Negative for CBFB, and positive for AML1/ETO	108	Survival
8	Female	May 2008	8	M2	CD34/CD19 2.2%, CD34 5.9%, CD19 2.7%, HLA-DR/CD13 3.6%, CD15 1.5%	Negative	Negative for 43 fusion genes	108	Survival
9	Male	February 2009	12	M4	Juvenile cells 64.1%, CD9 35.3%, CD11b 3.6%, CD34 57.4%, HLA-DR/CD13 54.5%	Negative	Negative for 43 fusion genes	108	Survival
10	Male	March 2010	8	M1	CD9 35.3%, CD11b 3.6%, CD34 57.4%, HLA-DR/CD13 54.5%	Negative	Negative for MLL	108	Survival
11	Female	October 2011	7	M4	CD13 43%, DR/CD13 40%, CD15/CD34 33%, CD34 50%, CD33 20%	Negative	Negative for PML-RAra, negative for AML1/ETO	108	Chemotherapy-related death

Table I. Continued.

Case	Sex	Admission date	Onsetage, years	Classification[a]	Immunophenotype	Chromosome analysis	Fusion gene	High-dose Ara-C, g/m^2	Outcome at 2022 (>5 years)
12	Female	December 2014	5	M4	One group of CD45-and one group of dimSSC-low juvenile cells (38.2 and 30.3%)	Negative	Positive for CBF-β/MYH11	108	Survival
13	Male	April 2015	4 years and 2 months	M2	CD34 72.5%, CD33 72.5%, CD13 71.7%, CD7 52.4%, HLA-DR7 4.3%, CD117 76.8%, CD15 43%	Negative	Negative for 43 fusion genes	108	Recurrence and death
14	Male	May 2015	4 years and 2 months	M6	CD15 0.8%, CD33 2.5%, HLA-DR 0.3%, CD34 0.3%, CD33 3.3%, CD15 1.1%, CD117 1.0%, CD34 1.9%, MPO 0.8%, HLA-DR 1.9%, CD11b 1.0%	Negative	Negative for 43 fusion genes	108	Survival
15	Male	April 2012	2	M5	DR/CD13 21%, CD15/CD34 15%, CD34 29%, CD34/CD14 8%, CD33/CD11b 23%, CD33 33%, CD4 36%	Negative	Negative for 43 fusion genes	108	Recurrence and death

[a](27).

without) (16), but the outcomes are still not satisfactory. Cytarabine, daunorubicin and etoposide (ADE) is an effective induction regimen for pediatric patients with relapsed AML, and a study by Garg *et al* obtained 2-year EFS and OS rates of 29% (±7%) and 34% (±7%) at the first relapse, with a complete remission rate of 66% (17).

HDAC improves OS and relapse-free survival rates in induction therapy while reducing the relapse rate in consolidation therapy, especially for the favorable-risk group. In one study, patients randomly assigned HD cytarabine treatment obtained 6-year OS rates of 42.5%, compared with 38.7% for those receiving standard cytarabine (18). The median OS time of patients with AML in a study also using high-dose cytarabine in Brazil was 23.5 months for the M0, M1 and M2 subtypes, 97.7 months for M3, and 7.4 months for M4, M5, M6 and M7, with a poor prognosis in most patients (19).

It has been noted that Ara-C in a dosage of 3 g/m^2 twice daily provides a maximal therapeutic effect in consolidation chemotherapy for adult patients with AML, associated with grade 3-4 non-hematological toxicity (20), but the optimal dosage for pediatric patients with AML is still controversial. Studies have evaluated high-dose cytarabine in induction therapy for children with *de novo* AML in Japan, adopting HD-ADE therapy, and suggested that Ara-C in a dosage of 3 g/m^2 twice daily obtains a good outcome with improved disease-free survival rates (21). In Saudi Arabia, the 5-year OS rates for the low-risk, intermediate-risk and high-risk groups were 72.0±6.9, 59.8±6.2 and 45.1±7.4%, and the EFS rates were 50.5±8.0, 46.3±6.4 and 23.3±6.4% (22).

Notably, the HDCT regimen developed in this study is clinically safe and effective, with relatively low cost, as it successfully reached 5-year EFS and OS rates of 80%. It should be emphasized that this regimen not only has great therapeutic value, but that also its EFS and OS rates for pediatric AML reach the current international leading level, and even the international leading academic level for hematological malignancies. HDCT seems an optimal option for childhood leukemia with chemotherapy alone.

According to a summary of treatments for AML from 8 international organizations involving the Children's Oncology Group, Berlin-Frankfurt-Munster, the Italian Association of Pediatric Hematology Oncology, and the European Organization for Research and Treatment of Cancer, the 5-year EFS rate ranges from 55.5 to 77.7% (23-26). This indicates that in the world, the highest 5-year EFS rate reaches ~77%, which is the result of not only chemotherapy, but also immune and targeted therapy. Thus similarly high or slightly higher rates of long-term remission are achieved by more complex regimens. However, these may not be available in numerous parts of China, for various reasons, including difficulties in finding a fully matched donor for transplantation, expense of medical care and the presence of a number of complications. Another issue is that AML is prone to relapse. As in most developing countries, most Chinese people usually only accept chemotherapy for leukemia, so it is imperative to seek a low-cost and efficient chemotherapy regimen.

In conclusion, HDCT therapy is clinically safe, effective and relatively low cost, and thus should be strongly considered in limited access (remote) or underserved areas.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the privacy of the patients, but are available from the corresponding author on reasonable request.

Authors' contributions

ZiW designed the HDCT for pediatric AML and organized this team to implement the regimen among patients with AML hospitalized in the First Affiliated Hospital of Guangzhou Medical University (Guangzhou, China), and wrote the draft of the manuscript. ZeW is also an important contributor to the manuscript and was responsible for some of the 20-year follow-up and data analysis. As great contributors, YZ, JG, SW and DC applied HDCT in clinical practice for over a decade and contributed to the conception of the study. All authors read and approved the final manuscript. ZiW, ZeW, YZ, JG, SW and DC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. Informed consent was obtained from the patients parent's/legal guardians before initiation of the regimen, as this study followed the Declaration of Helsinki on medical protocol and ethics.

Patient consent for publication

No applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Pelcovits A and Niroula R: Acute myeloid leukemia: A review. R I Med J (2013) 103: 38-40, 2020.
2. Yi M, Li A, Zhou L, Chu Q, Song Y and Wu K: The global burden and attributable risk factor analysis of acute myeloid leukemia in 195 countries and territories from 1990 to 2017: Estimates based on the global burden of disease study 2017. J Hematol Oncol 13: 72, 2020.
3. Chennamadhavuni A, Lyengar V and Shimanovsky A: Leukemia. In: StatPearls [Internet]. Treasure Island (FL), StatPearls Publishing; 2022.
4. Song TY, Lee SH, Kim G, Baek HJ, Hwang TJ and Kook H: Improvement of treatment outcome over 2 decades in children with acute myeloid leukemia. Blood Res 53: 25-34, 2018.
5. Herzig RH, Wolff SN, Lazarus HM, Phillips GL, Karanes C and Herzig GP: High-dose cytosine arabinoside therapy for refractory leukemia. Blood 62: 361-369, 1983.

6. Hwang WL, Young JH, Gau JP, Hu HT and Tsai YT: DAE (daunorubicin, Ara-C, and etoposide) and intermediate dose Ara-C for remission induction and consolidation treatment of adult patients with acute myeloid leukemia. Am J Clin Oncol 15: 531-534, 1992.
7. Gessner A, Thomas M, Castro PG, Büchler L, Scholz A, Brümmendorf TH, Soria NM, Vormoor J, Greil J and Heidenreich O: Leukemic fusion genes MLL/AF4 and AML1/MTG8 support leukemic self-renewal by controlling expression of the telomerase subunit TERT. Leukemia 24: 1751-1759, 2010.
8. Nakamura H, Kuriyama K, Sadamori N, Mine M, Itoyama T, Sasagawa I, Matsumoto K, Tsuji Y, Asou N, Kageyama SI, *et al*: Morphological subtyping of acute myeloid leukemia with maturation (AML-M2): Homogeneous pink-colored cytoplasm of mature neutrophils is most characteristic of AML-M2 with t(8;21). Leukemia 11: 651-655, 1997.
9. Jirasek MA and Herrington JD: Cytarabine syndrome despite corticosteroid premedication in an adult undergoing induction treatment for acute myelogenous leukemia. J Oncol Pharm Pract 22: 795-800, 2016.
10. Moore AS, Kearns PR, Knapper S, Pearson AD and Zwaan CM: Novel therapies for children with acute myeloid leukaemia. Leukemia 27: 1451-1460, 2013.
11. Schweitzer J, Zimmermann M, Rasche M, von Neuhoff C, Creutzig U, Dworzak M, Reinhardt D and Klusmann JH: Improved outcome of pediatric patients with acute megakaryoblastic leukemia in the AML-BFM 04 trial. Ann Hematol 94: 1327-1336, 2015.
12. Rubnitz JE, Pounds S, Cao X, Jenkins L, Dahl G, Bowman WP, Taub JW, Pui CH, Ribeiro RC, Campana D and Inaba H: Treatment outcome in older patients with childhood acute myeloid leukemia. Cancer 118: 6253-6259, 2012.
13. Kaspers GJ, Zimmermann M, Reinhardt D, Gibson BE, Tamminga RY, Aleinikova O, Armendariz H, Dworzak M, Ha SY, Hasle H, *et al*: Improved outcome in pediatric relapsed acute myeloid leukemia: Results of a randomized trial on liposomal daunorubicin by the International BFM Study Group. J Clin Oncol 31: 599-607, 2013.
14. Abrahamsson J, Forestier E, Heldrup J, Jahnukainen K, Jónsson OG, Lausen B, Palle J, Zeller B and Hasle H: Response-guided induction therapy in pediatric acute myeloid leukemia with excellent remission rate. J Clin Oncol 29: 310-315, 2011.
15. Rubnitz JE: Current management of childhood acute myeloid leukemia. Paediatr Drugs 19: 1-10, 2017.
16. Pollard JA, Guest E, Alonzo TA, Gerbing RB, Loken MR, Brodersen LE, Kolb EA, Aplenc R, Meshinchi S, Raimondi SC, *et al*: Gemtuzumab ozogamicin improves event-free survival and reduces relapse in pediatric KMT2A-Rearranged AML: Results from the phase III Children's Oncology Group Trial AAML0531. J Clin Oncol 39: 3149-3160, 2021.
17. Garg A, Ganguly S, Vishnubhatla S, Chopra A and Bakhshi S: Outpatient ADE (cytarabine, daunorubicin, and etoposide) is feasible and effective for the first relapse of pediatric acute myeloid leukemia: A prospective, phase II study. Pediatr Blood Cancer 67: e28404, 2020.
18. Willemze R, Suciu S, Meloni G, Labar B, Marie JP, Halkes CJ, Muus P, Mistrik M, Amadori S, Specchia G, *et al*: High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: Results of the EORTC-GIMEMA AML-12 trial. J Clin Oncol 32: 219-228, 2014.
19. Li W, Gong X, Sun M, Zhao X, Gong B, Wei H, Mi Y and Wang J: High-dose cytarabine in acute myeloid leukemia treatment: A systematic review and meta-analysis. PLoS One 9: e110153, 2014.
20. Padilha SL, Souza EJ, Matos MC and Domino NR: Acute myeloid leukemia: Survival analysis of patients at a university hospital of Parana. Rev Bras Hematol Hemoter 37: 21-27, 2015.
21. Wu D, Duan C, Chen L and Chen S: Efficacy and safety of different doses of cytarabine in consolidation therapy for adult acute myeloid leukemia patients: A network meta-analysis. Sci Rep 7: 9509, 2017.
22. Jastaniah W, Al Ghemlas I, Al Daama S, Ballourah W, Bayoumy M, Al-Anzi F, Al Shareef O, Alsultan A, Abrar MB and Al Sudairy R: Clinical characteristics and outcome of childhood de novo acute myeloid leukemia in Saudi Arabia: A multicenter SAPHOS leukemia group study. Leuk Res 49: 66-72, 2016.
23. Pession A, Masetti R, Rizzari C, Putti MC, Casale F, Fagioli F, Luciani M, Lo Nigro L, Menna G, Micalizzi C, *et al*: Results of the AIEOP AML 2002/01 multicenter prospective trial for the treatment of children with acute myeloid leukemia. Blood 122: 170-178, 2013.
24. Creutzig U, Zimmermann M, Dworzak MN, Ritter J, Schellong G and Reinhardt D: Development of a curative treatment within the AML-BFM studies. Klin Padiatr 225 (Suppl 1): S79-S86, 2013.
25. Creutzig U, Zimmermann M, Bourquin JP, Dworzak MN, Fleischhack G, Graf N, Klingebiel T, Kremens B, Lehrnbecher T, von Neuhoff C, *et al*: Randomized trial comparing liposomal daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: Results from Study AML-BFM 2004. Blood 122: 37-43, 2013.
26. Cooper TM, Franklin J, Gerbing RB, Alonzo TA, Hurwitz C, Raimondi SC, Hirsch B, Smith FO, Mathew P, Arceci RJ, *et al*: AAML03P1, a pilot study of the safety of gemtuzumab ozogamicin in combination with chemotherapy for newly diagnosed childhood acute myeloid leukemia: A report from the Children's Oncology Group. Cancer 118: 761-769, 2012.
27. Arber DA: The 2016 WHO classification of acute myeloid leukemia: What the practicing clinician needs to know. Semin Hematol 56: 90-95, 2019.