

World Journal of *Clinical Cases*

World J Clin Cases 2020 November 26; 8(22): 5496-5834



EDITORIAL

- 5496 Is Dynesys dynamic stabilization system superior to posterior lumbar fusion in the treatment of lumbar degenerative diseases?
Peng BG, Gao CH

MINIREVIEWS

- 5501 COVID-19: A review of what radiologists need to know
Tang L, Wang Y, Zhang Y, Zhang XY, Zeng XC, Song B
- 5513 Holistic care model of time-sharing management for severe and critical COVID-19 patients
Yang B, Gao Y, Kang K, Li J, Wang L, Wang H, Bi Y, Dai QQ, Zhao MY, Yu KJ

ORIGINAL ARTICLE**Case Control Study**

- 5518 Bioequivalence of two esomeprazole magnesium enteric-coated formulations in healthy Chinese subjects
Liu ZZ, Ren Q, Zhou YN, Yang HM
- 5529 Osteoprotegerin, interleukin and hepatocyte growth factor for prediction of diabetes and hypertension in the third trimester of pregnancy
Huang SJ, Wang HW, Wu HF, Wei QY, Luo S, Xu L, Guan HQ

Retrospective Study

- 5535 High serum lactate dehydrogenase and dyspnea: Positive predictors of adverse outcome in critical COVID-19 patients in Yichang
Lv XT, Zhu YP, Cheng AG, Jin YX, Ding HB, Wang CY, Zhang SY, Chen GP, Chen QQ, Liu QC
- 5547 Risk factors analysis of prognosis of adult acute severe myocarditis
Zhang Q, Zhao R
- 5555 Sonographic features of umbilical vein recanalization for a Rex shunt on cavernous transformation of portal vein in children
Zhang YQ, Wang Q, Wu M, Li Y, Wei XL, Zhang FX, Li Y, Shao GR, Xiao J

Clinical Trials Study

- 5564 Gemcitabine plus concurrent irreversible electroporation *vs* gemcitabine alone for locally advanced pancreatic cancer
Ma YY, Leng Y, Xing YL, Li HM, Chen JB, Niu LZ

Observational Study

- 5576** No significant association between dipeptidyl peptidase-4 inhibitors and adverse outcomes of COVID-19
Zhou JH, Wu B, Wang WX, Lei F, Cheng X, Qin JJ, Cai JJ, Zhang X, Zhou F, Liu YM, Li HM, Zhu LH, She Z, Zhang X, Yang J, Li HL

META-ANALYSIS

- 5589** Interobserver agreement for contrast-enhanced ultrasound of liver imaging reporting and data system: A systematic review and meta-analysis
Li J, Chen M, Wang ZJ, Li SG, Jiang M, Shi L, Cao CL, Sang T, Cui XW, Dietrich CF

CASE REPORT

- 5603** CLAG-M chemotherapy followed by umbilical cord blood stem cell transplantation for primary refractory acute myeloid leukaemia in a child: A case report
Huang J, Yang XY, Rong LC, Xue Y, Zhu J, Fang YJ
- 5611** Multiple schwannomas with pseudoglandular element synchronously occurring under the tongue: A case report
Chen YL, He DQ, Yang HX, Dou Y
- 5618** Primary myelofibrosis with concurrent *CALR* and *MPL* mutations: A case report
Zhou FP, Wang CC, Du HP, Cao SB, Zhang J
- 5625** Endometrial stromal sarcoma extending to the pulmonary artery: A rare case report
Fan JK, Tang GC, Yang H
- 5632** Malignant acanthosis nigricans with Leser-Trélat sign and tripe palms: A case report
Wang N, Yu PJ, Liu ZL, Zhu SM, Zhang CW
- 5639** Gastric plexiform fibromyxoma: A case report
Pei JY, Tan B, Liu P, Cao GH, Wang ZS, Qu LL
- 5645** Rectoseminal vesicle fistula after radical surgery for rectal cancer: Four case reports and a literature review
Xia ZX, Cong JC, Zhang H
- 5657** Azacitidine decreases reactive oxygen species production in peripheral white blood cells: A case report
Hasunuma H, Shimizu N, Yokota H, Tatsuno I
- 5663** Oral granuloma in a pediatric patient with chronic graft-versus-host disease: A case report
Uesugi A, Tsushima F, Kodama M, Kuroshima T, Sakurai J, Harada H
- 5670** Intrahepatic biliary cystadenoma: A case report
Xu RM, Li XR, Liu LH, Zheng WQ, Zhou H, Wang XC
- 5678** Gene diagnosis of infantile neurofibromatosis type I: A case report
Li MZ, Yuan L, Zhuo ZQ

- 5684** Localized amyloidosis affecting the lacrimal sac managed by endoscopic surgery: A case report
Song X, Yang J, Lai Y, Zhou J, Wang J, Sun X, Wang D
- 5690** Endoscopic resection of benign esophageal schwannoma: Three case reports and review of literature
Li B, Wang X, Zou WL, Yu SX, Chen Y, Xu HW
- 5701** Bouveret syndrome masquerading as a gastric mass-unmasked with endoscopic luminal laser lithotripsy: A case report
Parvataneni S, Khara HS, Diehl DL
- 5707** Nonhypertensive male with multiple paragangliomas of the heart and neck: A case report
Wang Q, Huang ZY, Ge JB, Shu XH
- 5715** Completed atrioventricular block induced by atrial septal defect occluder unfolding: A case report
He C, Zhou Y, Tang SS, Luo LH, Feng K
- 5722** Clinical characteristics of adult-type annular pancreas: A case report
Yi D, Ding XB, Dong SS, Shao C, Zhao LJ
- 5729** Port-site metastasis of unsuspected gallbladder carcinoma with ossification after laparoscopic cholecystectomy: A case report
Gao KJ, Yan ZL, Yu Y, Guo LQ, Hang C, Yang JB, Zhang MC
- 5737** Gonadal dysgenesis in Turner syndrome with Y-chromosome mosaicism: Two case reports
Leng XF, Lei K, Li Y, Tian F, Yao Q, Zheng QM, Chen ZH
- 5744** Gastric mixed adenoma-neuroendocrine tumor: A case report
Kohno S, Aoki H, Kato M, Ogawa M, Yoshida K
- 5751** Sebaceous lymphadenocarcinoma of the parotid gland: A case report
Hao FY, Wang YL, Li SM, Xue LF
- 5758** Misdiagnosis of ligamentoid fibromatosis of the small mesenteric: A case report
Xu K, Zhao Q, Liu J, Zhou D, Chen YL, Zhu X, Su M, Huang K, Du W, Zhao H
- 5765** Intraoperative care of elderly patients with COVID-19 undergoing double lung transplantation: Two case reports
Wu Q, Wang Y, Chen HQ, Pan H
- 5773** Amelioration of cognitive impairment following growth hormone replacement therapy: A case report and review of literature
Liu JT, Su PH
- 5781** Early colon cancer with enteropathy-associated T-cell lymphoma involving the whole gastrointestinal tract: A case report
Zhang MY, Min CC, Fu WW, Liu H, Yin XY, Zhang CP, Tian ZB, Li XY

- 5790** Bleeding of two lumbar arteries caused by one puncture following percutaneous nephrolithotomy: A case report
Liu Q, Yang C, Lin K, Yang D
- 5795** Hemorrhagic fever with renal syndrome complicated with aortic dissection: A case report
Qiu FQ, Li CC, Zhou JY
- 5802** Robot-assisted laparoscopic pyeloureterostomy for ureteropelvic junction rupture sustained in a traffic accident: A case report
Kim SH, Kim WB, Kim JH, Lee SW
- 5809** Large leiomyoma of lower esophagus diagnosed by endoscopic ultrasonography-fine needle aspiration: A case report
Rao M, Meng QQ, Gao PJ
- 5816** Endoscopic reduction of colocolonic intussusception due to metastatic malignant melanoma: A case report
Kasuga K, Sakamoto T, Takamaru H, Sekiguchi M, Yamada M, Yamazaki N, Hashimoto T, Uraoka T, Saito Y
- 5821** Usefulness of ultrasonography to assess the response to steroidal therapy for the rare case of type 2b immunoglobulin G4-related sclerosing cholangitis without pancreatitis: A case report
Tanaka Y, Kamimura K, Nakamura R, Ohkoshi-Yamada M, Koseki Y, Mizusawa T, Ikarashi S, Hayashi K, Sato H, Sakamaki A, Yokoyama J, Terai S

LETTER TO THE EDITOR

- 5831** Is positivity for hepatitis C virus antibody predictive of lower risk of death in COVID-19 patients with cirrhosis?
Mangia A, Cenderello G, Verucchi G, Ciancio A, Fontana A, Piazzolla V, Minerva N, Squillante MM, Copetti M

ABOUT COVER

Peer-reviewer of *World Journal of Clinical Cases*, Dr. Galiatsatos Aristidis is an Associate Professor, Department of Biomedical Sciences, Division of Dental Technology, University of West Attica. After graduating from the Faculty of Dentistry of University of Thessaloniki in 1988, he completed his PhD in the Dental Prosthodontics Department of Athens University in 1996. From 1988 to 2005, he continued his professional training in the University of Athens as a Research Fellow in Prosthodontics. During the 1998-1999 academic year, he was hired as a paid research scientist in the same subject area. In 2009, he rose to Assistant and then Associate Professor in the University of West Attica. From September 2019, he has served as Director of the Division of Dental Technology. (L-Editor: Filipodia)

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INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJCC* as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ji-Hong Liu*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lai Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

November 26, 2020

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INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

CLAG-M chemotherapy followed by umbilical cord blood stem cell transplantation for primary refractory acute myeloid leukaemia in a child: A case report

Jie Huang, Xiao-Yun Yang, Liu-Cheng Rong, Yao Xue, Jun Zhu, Yong-Jun Fang

ORCID number: Jie Huang 0000-0002-8652-4934; Xiao-Yun Yang 0000-0003-4135-6081; Liu-Cheng Rong 0000-0002-9517-4358; Yao Xue 0000-0002-1592-3225; Jun Zhu 0000-0001-9703-7464; Yong-Jun Fang 0000-0002-1081-6471.

Author contributions: Huang J reviewed the literature and contributed to manuscript drafting; Yang XY, Rong LC and Xue Y collected clinical data and contributed to manuscript drafting; Zhu J performed laboratory analysis and drafted the manuscript; Fang YJ was responsible for the revision of the manuscript for important intellectual content; All authors issued final approval for the version to be submitted.

Supported by the National Natural Science Foundation of China, No. 81670155.

Informed consent statement:

Written informed consent was obtained from the parents of the patient.

Conflict-of-interest statement: The authors state there is no conflict of interest.

CARE Checklist (2016) statement: Guidelines of the CARE Checklist

Jie Huang, Xiao-Yun Yang, Liu-Cheng Rong, Yao Xue, Jun Zhu, Yong-Jun Fang, Department of Haematology and Oncology, Children's Hospital of Nanjing Medical University, Nanjing 210008, Jiangsu Province, China

Corresponding author: Yong-Jun Fang, MD, PhD, Chief Doctor, Dean, Department of Haematology and Oncology, Children's Hospital of Nanjing Medical University, No. 72 Guangzhou Road, Nanjing 210008, Jiangsu Province, China. fyj322@189.cn

Abstract

BACKGROUND

The prognosis of paediatric primary refractory/relapsed acute myeloid leukaemia (R/R AML) remains poor. Intensive therapy is typically used as salvage treatment for those with R/R AML. No data are currently available about the use of the CLAG-M protocol as salvage therapy in paediatric patients with R/R AML.

CASE SUMMARY

An 8-year-old patient was diagnosed with acute myeloid leukaemia by bone marrow morphology and immunophenotype. The patient showed poor response to two cycles of induction therapy with 60% blast cells in the bone marrow after the second induction cycle. The patient achieved complete remission after being treated with the CLAG-M protocol as salvage therapy before undergoing umbilical cord blood stem cell transplantation. Morphological complete remission with haematological recovery has hitherto been maintained over 4 mo. Abnormal gene mutations detected at diagnosis were undetectable after haematopoietic stem cell transplantation.

CONCLUSION

Here we present a paediatric patient with primary refractory acute myeloid leukaemia who was successfully treated with the CLAG-M protocol. Given the positive results of the presented patient, large-scale clinical studies are required to assess the role of the CLAG-M protocol in the salvage treatment of refractory or relapsed AML in childhood.

Key Words: Acute myeloid leukaemia; CLAG-M protocol; Salvage therapy; Refractory; child; Case report

(2016) have been adopted.

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Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 1, 2020

Peer-review started: January 1, 2020

First decision: September 29, 2020

Revised: October 5, 2020

Accepted: October 19, 2020

Article in press: October 19, 2020

Published online: November 26, 2020

P-Reviewer: Biondi A, Pérez-Campo FM

S-Editor: Zhang H

L-Editor: Filipodina

P-Editor: Liu JH



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Core Tip: The outcome of refractory/relapsed acute myeloid leukaemia (R/R AML) in childhood remains poor. A boy with primary refractory AML achieved complete remission (CR) after being treated with one cycle of the CLAG-M protocol as salvage therapy. Umbilical cord blood stem cell transplantation was carried out after CR. The patient remains in complete remission without previous genetic abnormalities. The CLAG-M protocol might be an effective and tolerable salvage regimen and a bridge to haematopoietic stem cell transplantation in R/R AML. Additionally, we focus our literature review on the role of cladribine-based protocols in paediatric and adult R/R AML patients.

Citation: Huang J, Yang XY, Rong LC, Xue Y, Zhu J, Fang YJ. CLAG-M chemotherapy followed by umbilical cord blood stem cell transplantation for primary refractory acute myeloid leukaemia in a child: A case report. *World J Clin Cases* 2020; 8(22): 5603-5610

URL: <https://www.wjgnet.com/2307-8960/full/v8/i22/5603.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v8.i22.5603>

INTRODUCTION

The outcome of newly diagnosed paediatric acute myeloid leukaemia (AML) has markedly improved in past decades. The long-term survival of childhood AML has reached 70% with advances in first-line chemotherapy, haematopoietic stem cell transplantation (HSCT) and supportive care^[1]. Despite the impressive improvement in outcome, the prognosis of children with refractory/relapsed acute myeloid leukaemia (R/R AML) is still poor. There is no uniform salvage therapy for paediatric R/R AML. Intensified conventional therapy and new combinations have been used to achieve remission or second remission. Salvage treatment also serves as a bridge to HSCT.

Purine nucleoside analogue (PNA) combined with cytarabine (Ara-C) and granulocyte colony-stimulating factor (G-CSF), such as in the fludarabine, Ara-C and G-CSF (FLAG) protocol, has been widely used in both paediatric and adult R/R AML. Cladribine (2-CdA, 2-chloro-2'-deoxyadenosine) is one of PNAs approved for the treatment of haematological malignancies. Early clinical trials showed notable antileukaemic activity of cladribine used as a single agent in paediatric patients with R/R AML^[2]. Because of the impressive results of initial trials in paediatric patients, the use of 2-CdA has expanded from a single drug to different combination regimens with other agents. Multiple studies of cladribine-based regimens have been carried out in adults with R/R AML. To date, the most promising 2-CdA-based protocols in adult patients have been CLAG (2-CdA, Ara-C and G-CSF) and its derivative regimen CLAG-M (2-CdA, Ara-C, G-CSF and mitoxantrone), which was first reported by the Polish adult leukaemia group (PALG)^[3].

Data about the use of the CLAG-M protocol as salvage therapy in paediatric R/R AML is rarely available. We successfully treated a paediatric patient with primary refractory AML using the CLAG-M protocol followed by umbilical cord blood stem cell transplantation. This article discusses the clinical efficacy and toxicity of the CLAG-M protocol in refractory paediatric AML as salvage therapy. Written informed consent was obtained from the parents of the patient, and the study was approved by our institutional ethics committee.

CASE PRESENTATION

Chief complaints

An 8-year-old boy was admitted to the Department of Haematology and Oncology, Children's Hospital of Nanjing Medical University because of fever and enlargement of cervical lymph nodes.

History of present illness

The patient's symptom of fever started 5 d prior with gradually enlarged lymph nodes.

History of past illness

The patient had a free previous medical history.

Personal and family history

The parents denied any special personal or family history of leukaemia or other disease.

Physical examination

Physical examination showed pallor, cervical lymphadenopathy and splenomegaly.

Laboratory examinations

Peripheral blood count revealed hyperleukocytosis (white blood cell $103.8 \times 10^9/L$), anaemia (haemoglobin 74 g/L) and thrombocytopenia (platelets $56 \times 10^9/L$), while 70% blast cells were detected in peripheral blood smears with hypercellularity. Morphological examination of bone marrow aspirate showed 78% blast cells (Figure 1). Immunophenotypic analysis demonstrated that blast cells were positive for CD33 (96.70%), CD13 (57.55%), CD11b (18.20%), CD64 (19.00%), CD15 (31.70%), GPA (11.50%) and CD117 (85.10%). Normal karyotype, a heterozygous synonymous mutation (c.1107A>G) in exon 7 of the *WT1* gene and a heterozygous missense mutation (c.37G>T) in the N-terminal codon 13 of the *KRAS* gene were observed by genetic analysis.

Imaging examinations

An initial imaging evaluation with computed tomography scan revealed cervical lymphadenopathy and splenomegaly.

FINAL DIAGNOSIS

The diagnosis of AML (M2) was established.

TREATMENT

After the diagnosis of AML (M2), we administered induction chemotherapy to the patient using the daunorubicin, cytarabine and homoharringtonine regimen. Blast cells were not observed in cerebrospinal fluid after cytological examination. Bone marrow aspiration was performed 14 d after the first 7-d induction therapy and suggested no response with 79% blast cells. Treatment with idarubicin, cytarabine and homoharringtonine was initiated immediately as the second induction therapy. The patient still had a poor response with 10% blast cells and hypoplasia on day 15 and 60% blast cells in the bone marrow on day 21 after the second induction cycle. Then the patient was treated with the CLAG regimen combined with mitoxantrone as salvage therapy. The CLAG-M protocol herein consisted of cladribine (5 mg/m^2 intravenously in 2 h from day 1 to day 5), granulocyte colony-stimulating factor ($300 \text{ } \mu\text{g/m}^2$ hypodermic injection from day 0 to day 5), cytarabine (1 g/m^2 in 3 h intravenously infusions) and mitoxantrone (10 mg/m^2 intravenously daily for 3 d) (Figure 2). Routine bone marrow aspiration was done on day 15 after completion of the CLAG-M regimen. The patient achieved complete remission (CR) with 2% blast cells in the bone marrow but had severe bone marrow suppression after salvage therapy, and the duration of neutropenia was 14 d. The patient experienced febrile neutropenia, pneumonia and acroposthitis. The infection complications were controlled using antibiotics. He received six units of packed red cells and five units of platelets due to bone marrow suppression. Other nonhaematological toxicities associated with CLAG-M were mild. Given that matched sibling donors were not available, the patient underwent haematopoietic stem cell transplantation after salvage therapy using unrelated umbilical cord blood (10/10 matched). The myeloablative conditioning protocol included cytarabine, busulfan, fludarabine and cyclophosphamide (Figure 3). The prophylactic treatment for graft-versus-host disease

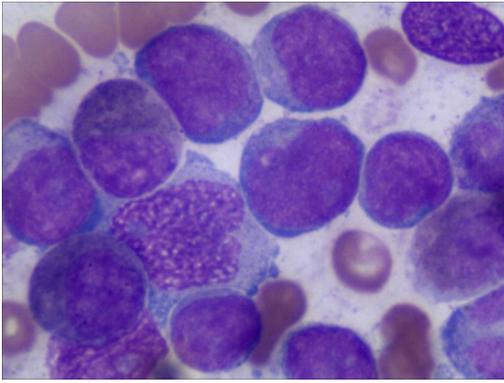


Figure 1 Blast cells in bone marrow at diagnosis.



Figure 2 CLAG-M protocol. Ara-C: Cytarabine; BM: Bone marrow; G-CSF: Granulocyte colony-stimulating factor; MIT: Mitoxantrone.

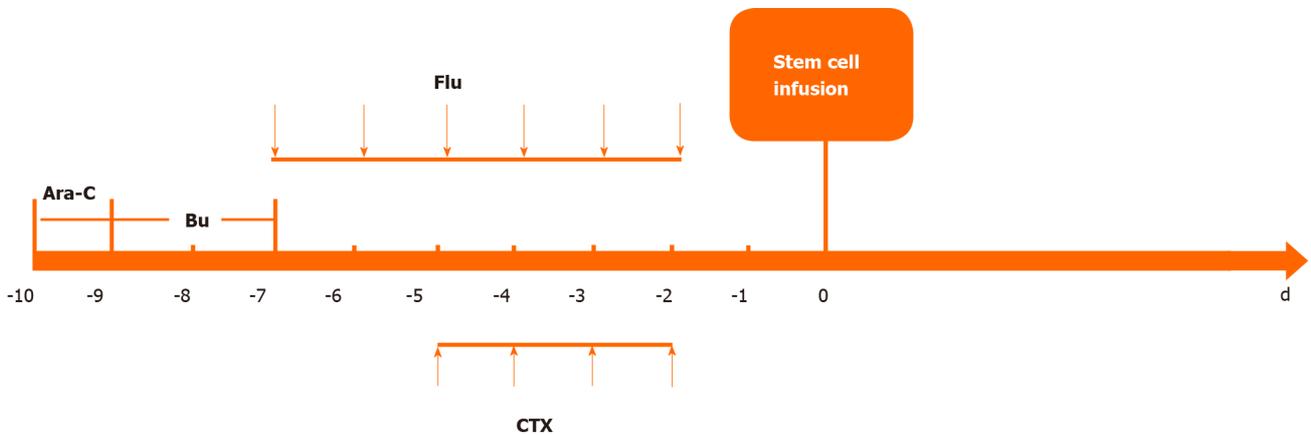


Figure 3 Conditioning protocol for umbilical cord blood stem cell transplantation. Ara-C: Cytarabine 1.5 g/m² intravenously (q12 h, day -10 to day -9); Bu: Busulfan 0.8 mg/kg (q6 h × 12, day -9 to day -7); CTX: Cyclophosphamide 50 mg/kg intravenously (qd × 4 d); Flu: Fludarabine 30 mg/m² (qd × 6 d).

(GVHD) consisted of mycophenolate mofetil and cyclosporine A. Transplantation-related toxicity was evidenced by perianal soft tissue infection and febrile neutropenia. Engraftment syndrome and grade II acute skin GVHD occurred but were alleviated by the use of systemic steroids.

OUTCOME AND FOLLOW-UP

Bone marrow assessment 30 d post-HSCT found morphological remission to be complete and both *WT1* and *KRAS* mutation negative. To date, over 60 d after transplantation, no other adverse effects have been detected, and complete graft chimerism has been achieved. Post-HSCT immunosuppressive treatment is tapering according to the control of GVHD. The status of primary disease and transplantation-

related complications are under close monitoring.

DISCUSSION

R/R AML remains the leading cause of failed treatment in children with AML. Some new chemotherapy regimens promise to be effective in this population. We chose the CLAG-M protocol to treat this patient with primary refractory paediatric AML for several reasons. First, the synergistic antileukaemic effect between cytarabine and cladribine was detected *in vivo* and *in vitro*^[4]. 2-CdA augments the cytotoxic effect of cytarabine by increasing the accumulation of cytarabine triphosphate, the active form of Ara-C. Second, given the fundamental premises, a phase II study from the PALG reported significant efficacy of the CLAG-M protocol in adult R/R AML^[5]. Third, the combination of cladribine and cytarabine was found to be effective as salvage therapy for refractory multisystem Langerhans cell histiocytosis^[6], which is also classified as a “myeloproliferative neoplasm”^[7].

In the past, the combination of cladribine and anthracycline was the backbone of treatment for AML. The cladribine-based regimen is one of the aggressive treatment options for adult R/R AML in recent recommendations from the National Comprehensive Cancer Network^[8]. One of the earliest studies of cladribine was performed by Santana *et al*^[9] in 1991. After being treated with single-agent 2-CdA, 47% of 18 paediatric patients with R/R AML achieved CR^[9].

Clinical trials have expanded to different cladribine-based combination regimens. Data from studies of paediatric AML supported cladribine-based regimens showed significant antileukaemic activity in this population. Although Rubnitz *et al*^[10] reported a disappointing response in eight patients with R/R AML who were pretreated with 2-CdA and Ara-C, the results of the St. Jude AML97 trial indicated that the combination of cladribine and cytarabine as window therapy before standard induction therapy was effective for newly diagnosed paediatric AML^[11]. A report from St. Jude Children’s Research Hospital showed that dose-escalating 2-CdA combined with topotecan yielded a CR rate of 35% in 26 children with R/R AML^[12]. A phase II study of 2-CdA plus idarubicin as salvage therapy for paediatric R/R AML showed an overall response rate of 51%^[13].

Several researchers carried out similar trials in adult AML patients. PALG first reported the use of the CLAG protocol for adults with R/R AML in 2003^[14]. A later study by PALG reported that CLAG-M led to a CR rate of 58% in 114 adult R/R AML patients^[3]. A retrospective study by Price *et al*^[15] concluded that the CLAG protocol achieved a higher CR rate in first-relapsed adult AML patients compared with the mitoxantrone, etoposide and cytarabine protocol (36.8% *vs* 25.9%). Seligson *et al*^[16] also found that the addition of cladribine to traditional AML induction therapy was beneficial to adult AML patients. Another study suggested that patients with *de novo* AML who had achieved CR at first induction therapy had a better survival rate when treated with the cladribine-based protocol than a fludarabine-based protocol^[17].

CLAG was equally effective to the FLAG protocol in R/R AML patients, while subgroup analysis disclosed that CLAG had a higher CR in those with second or higher salvage therapy^[18]. These data indicate that the cladribine-based protocol may raise the rate of CR in R/R AML patients, enabling these patients to undergo HSCT. A summary of key published data for 2-CdA-based treatment in paediatric and adult AML can be found in [Table 1](#).

Optimization of the salvage regimen is important to improve prognosis in paediatric R/R AML. A bridge to HSCT is the primary goal of salvage therapy. The efficacy of CLAG-M in paediatric R/R AML has not been reported before. Our patient showed a good response to the CLAG-M protocol and achieved CR after reinduction therapy. Studies on the combination of CLAG with other agents are ongoing. For instance, a later study suggested that the CLAG protocol combined with imatinib also had impressive activity in patients with high-risk AML^[19].

Genetic analysis of the patient revealed heterozygous mutations both in the *WT1* gene and the *KRAS* gene. About 76% of paediatric patients with AML had at least one gene mutation. *WT1* and *KRAS* gene mutations were found in over 10% of paediatric AML patients. *WT1* was associated with a poorer 3-yr overall survival and/or event-free survival^[20]. Results from another study also found *WT1* mutations were related to an inferior outcome in patients with cytogenetically normal AML, excluding patients with FLT3-ITD and those less than 3-years-old^[21]. *KRAS* mutation was found to be a distinct adverse prognostic factor in paediatric patients with mixed lineage leukaemia-rearranged AML, regardless of risk subgroup^[22]. However, whether the presence of the

Table 1 Cladribine-based chemotherapy in patients with acute myeloid leukaemia

Ref.	Patient number	Patient characteristic	Age	Regimen	Overall response rate, %	Number of patients who received subsequent HSCT	OS	Early death, n
Santana <i>et al</i> ^[2] , 1991	31	Paediatric, R/R ALL and AML	10 (1-21) yr	2- CdA	11% (25% in AML)	NR	NR	3
Santana <i>et al</i> ^[3] , 1992	24	Paediatric, R/R ALL and AML	11 (3-23) yr	2- CdA	CR: 47% (8/17), PR: 12% (2/17)	7	NR	0
Rubnitz <i>et al</i> ^[10] , 2004	8	Paediatric, R/R AML	5.0 (0.6-16.0) yr	2-CdA + Ara-C	0	0	NR	NR
Rubnitz <i>et al</i> ^[11] , 2009	102	Paediatric, ND AML	9.03 (0.05-21.00) yr	2-CdA + Ara-C, followed by DAE	CR 50%	32 (Allo-HSCT)9 (Auto-HSCT)	5-yr OS: 50.0% ± 5.5%	15
Inaba <i>et al</i> ^[12] , 2010	26	Paediatric, R/R AML	10.0 (1.0-19.0) yr	2-CdA + Topotecan	CR 34.6% PR 30.4%	8	Long-term survival: 19.2%	4
Chaleff <i>et al</i> ^[13] , 2012	104	Paediatric, R/R	75 (33-95) mo	2- CdA + IDA	51%	NR	26% at 2 yr	5
Wrzesien-Kus <i>et al</i> ^[14] , 2003	58	Adult, R/R	45 (18-67) yr	CLAG	50%	2 (Allo-HSCT)4 (Auto-HSCT)	42% at 1 yr	10
Wierzbowska <i>et al</i> ^[3] , 2008	118	Adult, R/R	45 (20-66) yr	CLAG-M	58%	20 (Allo-HSCT)6 (Auto-HSCT)	14% at 4 yr	7
Price <i>et al</i> ^[15] , 2010	162	Adult, R/R	CLAG: 55.1 (23.0-83.0) yr, MEC: 55.0 (21.0-90.0) yr	CLAG/MEC	CR: 37.9% (CLAG), CR: 23.8% (MEC)	NR	Median survival: 11.0 mo (CLAG), 4.5 mo (MEC)	9.4% (CLAG), 10.9% (MEC)
Park <i>et al</i> ^[17] , 2016	120	Adult, R/R	56.6 (19.0-83.0) yr	CLAG/CLAG-M/FLAG/FLAGI/mFLAI	CR: 62.7% (CLAG/CLAGM), CR: 61.4% (FLAG/FLAGI/mFLAI)	33	34.0% at 1 yr, 21.4% at 5 yr	NR
Bao <i>et al</i> ^[18] , 2017	103	Adult, R/R	CLAG: 51.0 ± 17.7 yr, FLAG: 48.8 ± 17.5 yrs	CLAG/FLAG	CR: 61.7% (CLAG), CR: 48.7% (FLAG)	11 (CLAG), 10 (FLAG)	CLAG: 45.5% at 1 yr, 35.3% at 3 yr, FLAG: 35.4% at 1 yr, 26.8% at 3 yr	NR
Seligson <i>et al</i> ^[16] , 2018	37	Adult, ND	7 + 3 IA: 61 (27-79) yr, 7 + 3 + 5 IAC: 58 (36-71) yr	7 + 3 IA/ 7 + 3 + 5 IAC	CR: 42% (7 + 3 IA), CR: 34% (7 + 3 + 5 IAC)	NR	NR	NR
Mirza <i>et al</i> ^[19] , 2017	38	Adult, R/R	62 (26-79) yr	CLAG + Imatinib	CR: 37%, PR: 11%	8	11.1 mo (95%CI: 4.8-13.4 mo)	2

2-CdA: Cladribine; ALL: Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; Ara-C: Cytarabine; CI: Confidence interval; CLAG: Cladribine, cytarabine and granulocyte colony-stimulating factor; CLAG-M: Cladribine, cytarabine, granulocyte colony-stimulating factor and mitoxantrone; CR: Complete remission; DAE: doxorubicin hydrochloride, bevacizumab, and everolimus; FLAG: Fludarabine, cytarabine and granulocyte colony-stimulating factor; FLAGI: Fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin; HSCT: Haematopoietic stem cell transplantation; IA: Idarubicin and cytarabine; IAC: Idarubicin, cytarabine and cladribine; IDA: Idarubicin; MEC: Mitoxantrone, etoposide and cytarabine; mFLAI: Modified fludarabine, cytarabine, and attenuated-dose idarubicin; ND: Newly diagnosed; NR: Not reported; OS: Overall survival; PR: Partial remission; R/R: Refractory and/or relapse.

co-occurrence of *WT1* and *KRAS* mutations could increase the response rate to cladribine-based salvage therapy still remains unclear.

Chemotherapy alone is unlikely to be curative in patients with primary refractory or relapsed AML due to drug resistance. HSCT is often used after achievement of remission. Our patient received unrelated umbilical cord blood transplantation after complete remission. His bone marrow kept up a morphological CR after umbilical cord blood transplantation. Additionally, genetic abnormalities also disappeared. Haematologic toxicity was the most prominent toxicity in the cladribine-based regimen. Although cladribine has limited acute toxicities, there are no increased haematopoietic toxicities reported in paediatric patients or in patients aged over 60 years^[11,13,23]. Our patient also experienced approximately 2 wk of neutropenia and infections due to myelosuppression, but the infections were well controlled using antibacterial and antifungal agents. Other adverse events of the CLAG-M protocol were mild and tolerable. We would suggest using prophylactic antifungal agents during grade 3 to 4 neutropenia. This is the first case report of using the CLAG-M protocol in childhood R/R AML. Our patient successfully achieved complete remission before HSCT.

CONCLUSION

In conclusion, the CLAG-M protocol might be an effective and well-tolerated salvage regimen in R/R AML in childhood. Further studies on a large group of paediatric patients are warranted to investigate the efficacy of the CLAG-M protocol as salvage treatment or as a bridge to HSCT. Moreover, the possibility of a cladribine-based protocol being used as first line therapy in high-risk paediatric patients also needs further investigation. A study on the effectiveness and safety of the CLAG combined with anthracyclines in paediatric R/R AML has been launched in our hospital.

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