Clinical Case Reports

Open Access

CASE REPORT

Induction treatment of acute myeloid leukemia in an elderly patient with intramarrow injection/administration of cytarabine: first report of a case

Anwarul Islam

Division of Hematology/Oncology, Department of Medicine, Buffalo General Hospital, Room E 318, Buffalo, New York 14203

Correspondence
Anwarul Islam, Division of Hematology/Oncology, Department of Medicine, Buffalo General Hospital, Room E 318, Buffalo, NY 14203. Tel: +716 859 2360; Fax: +716 859 3659; E-mail: aislam@buffalo.edu

Funding Information
No sources of funding were declared for this study.

Received: 26 August 2015; Revised: 28 September 2015; Accepted: 1 October 2015

Clinical Case Reports **2015; 3(12): 1026–1029**

doi: 10.1002/ccr3.429

Key Clinical Message

We have used intramarrow injection/administration of cytarabine (Ara-C) instead of conventional intravenous approach to induce remission in an elderly patient with acute myelogenous leukemia. We show for the first time that the intramarrow injection of chemotherapeutic agents such as Ara-C can be used safely and effectively.

Keywords

Acute myelogenous leukemia, cytarabine (Ara-C), intra-marrow injection/administration.

Introduction

Chemotherapy, especially by intravenous administration, remains the primary modality of treatment for patients with leukemia, lymphoma, and other hematologic malignancies [1–3]. Ara-C and other antineoplastic agents, when administered intravenously, require high doses to achieve their goal. For younger patients, such treatment works well, but older patients cannot tolerate such intensive (high dose) chemotherapy. Thus, more effective and less toxic therapies or new methods of treatment for older patients with AML (acute myelogenous leukemia) who are not eligible for a standard intensive induction therapy are needed. With this view in mind and not in keeping with past and present practices [4] such as intravenous and subcutaneous injection, we have designed a new method of targeted therapy that delivers chemotherapeutic agents directly into the marrow cavity, thus intensifying the effects of Ara-C and thereby producing rapid destruction and elimination of the leukemic blast cells.

Chemotherapeutic agents, when given intravenously, are diluted multifold as they enter into the circulation and mix with approximately 5 L of circulating blood and as a result when they reach their target organ, particularly bone marrow, their effective concentration become much less than when they were injected intravenously. In addition, during their dispersion, they may also bind specifically or nonspecifically to proteins or other tissue components and become less effective. In addition, they may never reach the endosteal region and come in contact with the endosteal cells, according to some hypotheses, where leukemia originates [5, 6]. Furthermore, intramarrow injection not only delivers the active agent (s) directly into the bone marrow, thus providing direct contact with multitude of leukemic blast cells, but also bathes the endosteum.

Admittedly, an injection of chemotherapeutic agents into the hip bones or sternum, cannot directly affect other bone marrow sites, but agents released here are absorbed by venous sinusoids of this highly vascularized organ and ultimately reach distal bone marrow regions almost as effectively as by conventional (intravenous) methods of administration. Thus, the overall effect achieved by intramarrow therapeusis is a more intimate association/contact of the anticancer drug(s) with a large number of target cells and at a high concentration with

potential enhancement of antineoplastic activity. The present technique of direct intramarrow injection/administration of chemotherapeutic agents has the potential advantage of overcoming many of the disadvantages associated with the conventional intravenous therapy. In addition, it may also circumvent some of the physiological barriers that a blood-borne molecule has to encounter before it reaches its target cell. Furthermore, the total dose of Ara-C used is much smaller than that used in standard 7 + 3 protocol. Thus, the therapy-induced toxicity is lessened. If indeed this or similar intraosseous treatment becomes successful, then in the future, AML patients can be treated on an outpatient basis, thus reducing the toxicity and cost of hospitalization. This study may also serve as the basis for treatment in both young and old newly diagnosed patients with AML. Furthermore, this protocol may be exploited in the treatment of other hematologic malignancies such as multiple myeloma with Bortezomib.

Case Report

The patient, a 76-year-old white female, presented to the emergency room of hospital A with one month's history of generalized weakness, diarrhea, frequency of micturition, and decreased appetite. The patient also stated that she was sleeping almost 20 h a day and felt extremely lethargic. Her past medical history was significant for hypertension, diabetes mellitus, obesity, colitis, recto-vaginal fistula, GERD, asthma, cellulitis, nephrolithiasis, COPD, hiatal hernia, and atypical chest pain.

On physical examination, the patient was noted to be anemic, but she was not in acute distress. There was no jaundice, cyanosis, or edema. Her abdomen was soft and nontender. Bowel sounds were heard. Liver, spleen, and kidneys could not be palpated due to abdominal obesity. There was no palpable lymphadenopathy. Heart sounds were normal. The chest was clear to auscultation and her vital signs were stable. The patient was afebrile.

Laboratory investigations revealed White Blood Cell (WBC) 42.5 $\times$ 10^9/L, hemoglobin 7.3 g/dL with normal Mean Corpuscular Volume (MCV), and Mean Corpuscular Hemoglobin (MCH) and a platelet count of 31 $\times$ 10^9/L. The differential counts revealed 15% segmented forms, 5% bands, 60% blasts and 13% lymphocytes, and 7% nucleated red blood cells. The peripheral blood smear revealed a frankly leukemic blood picture. Morphologically, the blast cells appeared to be myeloblasts (Fig. 1).

The bone marrow aspirate and flow cytometry confirmed the diagnosis of acute myeloblastic leukemia. The bone marrow aspirate revealed a highly cellular marrow (95%) with 64.5% myeloblasts, 0.5% promyelocytes, 10% myelocytes, 5% metamyelocytes, 2% bands, 4% neutrophils, 1% monocytes, and 4% lymphocytes, 0% basophils, 0% eosinophils, 0% plasma cells, and 9% erythroid precursors. Flow cytometry studies on the bone marrow aspirate sample revealed an abnormal blast cell population (58% of total events), which was "positive CD 117 (partial), CD 33, CD 13 (dim), and CD 56 while negative for CD 34, HLA-DR, CD 10, CD 19, CD 20, CD 22, CD 14, CD 64, CD 1a, CD 2, CD 3, and CD 7. There was some possible dim CD 15 expression".

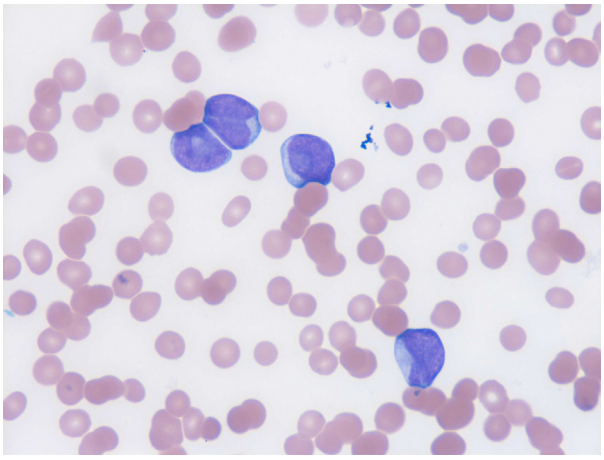

Figure 1. Peripheral blood smear showing immature myeloid cells (myeloblasts).

Cytogenetic studies revealed an extremely low mitotic index. Only 14 metaphase spreads were available, which showed a normal female karyotype of 46, XX. No apparent clonal chromosomal aberrations were detected.

Molecular studies revealed a NMP1 mutation in exon 12 of the gene. There was no evidence for either the FLT3 ITD or the codon 835/836 mutations.

After providing informed consent, the patient was treated with an intramarrow injection of Ara-C. The patient was premedicated with 100 mg of hydrocortisone and 50 mg of Benadryl intravenously half an hour before the intramarrow injection of Ara-C. The first injection of Ara-C (30 mg/m^2) was given into the right posterior ilium. The subsequent intramarrow injections of Ara-C (25 mg/m^2) were given into the sternum (each time a slightly different area of the sternum was chosen) once daily for 5 days. The patient tolerated the treatment procedure well and without any untoward effects, particularly nausea and vomiting which commonly occurs during Ara-C infusion.

On the day of first intramarrow injection, her WBC count was 71 $\times$ 10^9/L with 84% blast cells. Three days following the start of the treatment, her WBC count fell to 30 $\times$ 10^9/L and blast cell counts fell to 20%. Five days following the start of the treatment, her WBC count fell to 15 $\times$ 10^9/L and blast cell counts fell to 11%. At this

stage, the peripheral blood smear also showed the appearance of few mature granulocytes.

The patient thus showed a dramatic response to intramarrow injection of Ara-C, particularly with respect to a rapid elimination of blast cells from the peripheral blood and perhaps also from the bone marrow. However, because of multiple comorbidities and socio-economic condition, the patient's family decided to discontinue her therapy and opted for hospice care. The patient expired a few days after she entered into hospice care. This circumstance precluded the opportunity to continue with our intramarrow injection therapy of Ara-C as per planned protocol (once daily for 5–7 days every 4–6 weeks) as well as to obtain the follow-up bone marrow assessments.

Discussion

The optimal therapeutic approach for older (age ≥60 years) patients with AML is currently not known. In general, older AML patients have a poor prognosis and median overall survival rate is <1 year [7–9]. New methods or newer agents with decreased toxicities and improved survival are needed to treat elderly patients with AML [10–13].

We have used a new method of intramarrow injection/administration of Ara-C instead of the conventional intravenous or subcutaneous approach to induce remission in an elderly patient with AML. The approach of intramarrow injection/administration was chosen to provide a concentrated amount of chemotherapeutic agent (in this case Ara-C) directly into the marrow cavity of posterior ilium and sternum so that a large number of leukemic cells could be exposed to the chemotherapeutic agent. In addition, it was also postulated that a proportion of the injected chemotherapeutic agent into the hip bones or sternum, would also be absorbed via venous sinusoids and ultimately reach the malignant cells in distal bone marrow regions thus providing an enhanced and overall antineoplastic activity. The dose of Ara-C used (30 mg/m^2 on day 1 at the right posterior ilium and the subsequent intramarrow injections of Ara-C (25 mg/m^2) were given into the sternum once daily for 5 days) was considerably smaller than the standard 7 + 3 protocol (100 mg/m^2/day for 7 days along with daunorubicin on days 1–3). The schedule used for our patient is, in fact comparable to the low-dose (20 mg/m^2 sc for 10–14 days every 4–6 weeks) Ara-C protocol that is used for the treatment of elderly patients with AML [9, 12] or relapsed or refractory AML patients [14]. The only difference between the low-dose Ara-C treatment and our intraosseous protocol is that the latter provides direct contact of the leukemic cells with Ara-C, thus affording a maximum killing effect of the leukemic cells. The small dose of Ara-C used may also have reduced the toxicity of the drug particularly nausea and vomiting [15].

As the title implies, this is the first case in which we have used a new method (intramarrow injection/administration) of treating an elderly patient with AML. As a result, there are no biological studies assessing intramarrow injection of chemotherapeutic agents nor are there are any specific comparative studies between a standard Ara-C approach and the schedule reported.

Although this is a single patient where intramarrow therapy with Ara-C was used, this strategy seems to have worked in this particular case as evidenced by the fact that the leukemic blast cells were significantly reduced in number in the peripheral blood within days of starting the therapy. Clinically, the patient also felt better, and nausea and vomiting were absent. It is understood that a standardization of response criteria and treatment outcomes are required for the proper evaluation of treatment protocols for acute myeloid leukemia [16]. The brief and initial study of our patient, however, prevented this type of assessment.

Conflict of Interest

None declared.

References

1. Yates, J. W., H. J. Jr Wallace, R. R. Ellison, and J. F. Holland. 1973. Cytosine arabinoside (NSC-63878) and daunorubicin (NSC-83142) therapy in acute nonlymphocytic leukemia. Cancer Chemother. Rep. 57:485–488.
2. Sehn, L. H., J. Donaldson, M. Chhanabhai, C. Fitzgerald, K. Gill, R. Klasa. 2005. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J. Clin. Oncol. 23:5027–5033.
3. Smith, A. F., G. J. Morgan, and F. E. Davies. 2006. Bortezomib (Velcade™) in the treatment of multiple myeloma. Ther. Clin. Risk Manag. 3:271–279.
4. Estey, E. 2015. Why is progress in acute myeloid leukemia so slow? Semin. Hematol. 52:243–248.
5. Islam, A. 1992. The origin and spread of human leukemia. Med. Hypotheses 39:110–118.
6. Islam, A. 1985. Haemopoietic stem cell: a new concept. Leuk. Res. 9:141–151.
7. Estey, E. 2007. Acute myeloid leukemia and myelodysplastic syndromes in older patients. J. Clin. Oncol. 25:1908–1915.
8. Menzin, J., K. Lang, C. C. Earle, D. Kerney, and R. Mallick. 2002. The outcomes and costs of acute myeloid leukemia among the elderly. Arch. Intern. Med. 162:1597–1603.
9. Stone, R. M. 2002. The difficult problem of acute myeloid leukemia in the older adult. CA Cancer J. Clin. 52:363–371.

10. Burnett, A. K., D. Milligan, A. G. Prentice, A. H. Goldstone, M. F. McMullin, R. K. Hills, et al. 2007. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer 109:1114–1124.
11. Isidori, A., A. Venditti, L. Maurillo, F. Buccisano, F. Loscocco, and P. Manduzio. 2013. Alternative novel therapies for the treatment of elderly acute myeloid leukemia patients. Exp. Rev. Hematol. 6:767–784.
12. Fenaux, P., G. J. Mufti, E. H. Lindberg, V. Santini, N. Gattermann, U. Germing, et al. 2010. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J. Clin. Oncol. 28:562–569.
13. Kantarjian, H. M., X. G. Thomas, A. Dmoszynsks, A. Wierzbowska, G. Mazur, J. Mayer, et al. 2012. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J. Clin. Oncol. 30:2670–2677.
14. Zhang, W. G., F. X. Wang, Y. X. Chen, X. M. Cao, A. L. He, J. Liu, et al. 2007. Combination chemotherapy with low-dose cytarabine, homoharringtonine, and granulocyte colony-stimulating factor priming in patients with relapsed or refractory acute myeloid leukemia. Am. J. Hematol. 83:185–188.
15. Frei, E. III, J. N. Bickers, J. S. Hewlett, M. Lane, W. V. Leary, and R. W. Talley. 1969. Dose schedule and antitumor studies of arabinosyl cytosine. Cancer Res. 29:1325–1332.
16. Cheson, B. D., J. M. Bennett, K. J. Kopecky, T. Buchner, C. L. William, E. H. Estey, et al. 2003. Revised recommendation of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J. Clin. Oncol. 21:4642–4649.

