Acute Heart Failure in a Patient with Acute Myeloid Leukemia following Daunorubicin Treatment: a Case Report

Lawrence Druhan1*, Omotayo Fasan1 and Olivia R. Copelan1

1Levine Cancer Institute - Carolinas HealthCare System, Department of Hematologic Oncology and Blood Disorders, 1021 Morehead Medical Drive, Charlotte, NC 28204, USA

*Corresponding author: Lawrence Druhan, PhD, Levine Cancer Institute - Carolinas HealthCare System, Department of Hematologic Oncology and Blood Disorders, 1021 Morehead Medical Drive, Charlotte, NC 28204, USA. Tel: 704-355-0011; Fax: 980-442-3101; E-mail: lawrence.druhan@carolinashealthcare.org

Rec date: May 11, 2015; Acc date: June 02, 2015; Pub date: June 10, 2015

Abstract

Heart failure following anthracycline treatment is usually chronic, irreversible, and related to life time dose. We present a patient with Acute Myeloid Leukemia (AML) who developed Heart failure soon after dose intensified treatment with daunorubicin, with a decrease in Ejection Fraction (EF) from 60% to as low as 10% six months after initial treatment. The patient was managed medically, his EF increased to greater than 50%. With this improvement in EF the patient was treated with reinduction chemotherapy and proceeded to hematopoietic stem cell transplantation. Following transplantation, the patient again developed heart failure, which contributed to his death. While anthracycline dose intensification can be effective in the treatment of AML, there is a risk of heart failure which requires further study.

Keywords: Heart failure; Daunorubicin; Anthracycline; Acute myeloid leukemia

Introduction

Daunorubicin is an antitumor anthracycline antibiotic active in Acute Myeloid Leukemia (AML) and several other malignancies. Its main anticancer mechanisms appear to consist of intercalation into DNA inhibiting DNA replication and protein synthesis and generation of reactive oxygen species leading to DNA damage and lipid peroxidation [1]. Its major cumulative dose-limiting toxicity is congestive heart failure, typically insidious in onset after chronic anthracycline treatment, particularly with cumulative doses in excess of 500 mg/m2 [2]. Rarely, acute left ventricular failure has been described within a week of anthracycline administration and is usually fatal [3-5]. The development of acute heart failure does not appear to be dose related, however, the total dose administered during a day or course of treatment may affect late cardiotoxicity [6]. Recent evidence that anthracycline dose intensification in AML [7,8] improves survival has led to the routine administration of high doses over short time intervals, with limited published follow up of cardiac effects.

Case presentation

A 52 year old businessman was evaluated at an outside hospital emergency room for progressive fatigue, weakness and shortness of breath with exertion over the previous three weeks. He denied bone pain, fever, chills, bruising or bleeding. He had a history of polycystic kidney disease and was followed with annual labs including blood counts, which had been normal 6 months earlier. His CBC on presentation to the emergency room showed a white count of 1000/WL, Hb 7 g/dL and platelet count of 59,000/WL. Blasts were seen in his peripheral blood and he was transferred to Carolinas Medical Center where a bone marrow exam demonstrated 30% cellularity composed predominantly of myeloblasts with minimal differentiation. Cytogenetic analysis demonstrated a normal karyotype and wild type FLT3 and NPM1. Evaluation of the blast cells by flow cytometry demonstrated an immature myeloid phenotype with positivity for HLA-DR, CD34, CD117, CD13 (dim), CD33 (dim), and CD38. The echocardiogram showed an ejection fraction (EF) of 60% and the patient was treated with 7 days of cytarabine + 3 days (7 and 3) of anthracycline (90 mg/m2 daunorubicin daily for 3 days as reported [7,8]). At day 14, his marrow was hypocellular but consisted of mainly blasts. A repeat echocardiogram showed an ejection fraction (EF) of 60% and he was treated with a second round of 7+3 (45 mg/m2 daunorubicin daily for 3 days [7]). He subsequently developed congestive heart failure and sepsis with hypotension and his ejection fraction, 4 weeks after his initial induction, declined to 35%. Two weeks later his counts recovered and his bone marrow examination showed complete remission. He received two courses of high dose cytarabine, but the second course was complicated by sepsis and klebsiella bacteremia, and he spent a week critically ill in the medical ICU. A subsequent echocardiogram indicated an ejection fraction of 10% and no additional post-remission therapy was administered.

He was medically managed and shortly resumed desk-work 20 hours/week. His energy level and physical activity improved over several months. He gradually became stronger, worked full time and an echocardiogram seven months after cessation of chemotherapy showed an EF of 30%. Thirteen months after his initial diagnosis, his counts fell modestly and a marrow showed 10% myeloblasts; his ejection fraction by echocardiogram had further improved to 51%. With the marked improvement in EF, the patient received reinduction treatment with clofarabine, followed by an allogeneic transplant from his HLA matched sister using non-myeloablative conditioning with cyclophosphamide, fludarabine, and TBI with post-transplant cyclophosphamide for prevention of graft-versus-host disease. His post-transplant course was complicated by neutropenic fever, HHV6 viremia and heart failure with an EF of 20% 6 weeks after transplantation. He required intubation for respiratory failure, which was thought to be due to both cardiogenic and non-cardiogenic pulmonary edema, stemming from heart failure and pneumonitis with...
possible capillary leak. He was gradually improving and being weaned from the ventilator when he developed an episode of ventricular tachycardia followed by cardiac arrest. He expired three months after transplantation.

Discussion

Acute anthracycline induced cardiotoxicity, unlike the more common chronic form, is characterized by a transient decrease in ejection fraction, and the severity of the anthracycline induced cardiotoxicity can range from mild ventricular dysfunction to heart failure [9]. This case demonstrates acute cardiotoxicity, as evidenced by significant decrease in LV ejection fraction, within a few days of anthracycline and cytarabine administration.

Rarely, takotsubo cardiomyopathy has been associated with use of these agents [10,11], however in the presented case the resolution of the heart failure occurred over the course of months. The occurrence of acute anthracycline induced heart failure following a very high dose density of daunorubicin (405 mg/m² within a 3 week period) raises the important issue of whether this high dosage within a short time interval might increase the risks for the development of anthracycline cardiotoxicity.

This question is particularly timely because of recent evidence of the effectiveness and growing standard use of anthracycline dose intensification in AML [7,8,12]. Two studies reported that patients up to age 65 who receive daunorubicin 90 mg/m² for 3 days have a higher rate of complete remission and improved survival, without an increase in cardiac toxic effects, compared to those receiving 45 mg/m² [7,8].

Importantly, however, only 29 of 327 patients receiving 3 doses of 90 mg/m² received a second anthracycline containing induction treatment in one study [7] and anthracycline containing reinduction was not used in the second study [8].

In addition, it is not stated precisely how soon after the initial regimen these patients were treated or how many of these 29 patients were among the four patients in the high dose group who died as a result of cardiotoxicity (compared to none in the standard dose group) [7]. Additionally, there are indications that the efficacy of daunorubicin dose intensification is dependent upon the risk category of the disease under treatment [7,8,13,14].

While the doses and timing of anthracycline, as administered in this case, is according to guidelines [15], the risk of cardiotoxicity in patients receiving 270 mg/m² of daunorubicin followed shortly thereafter by 135 mg/m² of daunorubicin is not well defined. Moreover, the effectiveness of the “standard” approach of reinducing patients with residual AML at day 14 with 7+3 immediately has been recently questioned [16], further emphasizing that this standard approach may not be optimal.

Lastly, the cardiac effects of this dose-intense anthracycline administration is particularly concerning when one considers that many of these patients will eventually undergo hematopoietic cell transplantation, with its own risk of cardiac toxicity demonstrated to correlate with previous anthracycline dosages [17].

Following transplantation the risk of congestive heart failure is approximately 10 fold higher in individuals with ≥ 250 mg/m² of cumulative anthracycline exposure [17,18]. This case and the paucity of follow up data in patients receiving high dose anthracycline therapy for AML should inspire better studies of the cardiac effects of these anthracyline dose schedules.

Conclusion

It is important to recognize that unlike chronic anthracycline cardiotoxicity, the acute form may be reversible, as it was in this case. Following transplantation this patient again developed heart failure, which contributed to his death, emphasizing the risk of dose-intense anthracyclines.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Author’s contributions

ORC analyzed and interpreted patient data and was involved in writing manuscript. LJD interpreted data and was involved in writing the manuscript. OF interpreted data and edited the manuscript.

References

1. Gammella E, Maccarinelli F, Buratti P, Recalcati S, Cairo G (2014) The role of iron in anthracycline cardiotoxicity. Front Pharmacol 5: 25.
2. Carvalho FS, Burgeiro A, Garcia R, Moreno AJ, Carvalho RA, et al. (2014) Doxorubicin-induced cardiotoxicity: from bioenergetic failure and cell death to cardiomyopathy. Med Res Rev 34: 106-135.
3. Dazzi H, Kaufmann K, Follath F (2001) Anthracycline-induced acute cardiotoxicity in adults treated for leukaemia. Analysis of the clinico-pathological aspects of documented acute anthracycline-induced cardiotoxicity in patients treated for acute leukaemia at the university hospital of zurich, switzerland, between 1990 and 1996. Annals of oncology 12: 963-966.
4. Hayek ER, Speakman E, Rehmus E (2005) Acute doxorubicin cardiotoxicity. N Engl J Med 352: 2456-2457.
5. Yang SC, Chuang MH, Li DK (2010) The development of congestive heart failure and ventricular tachycardia after first exposure to idarubicin in a patient with acute myeloid leukaemia. Br J Clin Pharmacol 69: 209-211.
6. Lipshultz SE, Lipshitz SR, Mone SM, Goorin AM, Sallan SE, et al. (1995) Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 332: 1738-1743.
7. Fernandez HF, Sun Z, Yao X, Litzow MR, Luger SM, et al. (2009) Anthracycline dose intensification in acute myeloid leukaemia. N Engl J Med 361: 1249-1259.
8. Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, et al. (2009) High-dose daunorubicin in older patients with acute myeloid leukaemia. N Engl J Med 361: 1325-1328.
9. Raj S, Franco VI, Lipshultz SE (2014) Anthracycline-induced cardiotoxicity: A review of pathophysiology, diagnosis, and treatment. Curr Treat Options Cardiovasc Med 16: 315.
10. Goel S, Sharma A, Garg A, Chandra A, Shetty V (2014) Chemotherapy induced Takotsubo cardiomyopathy. World J Clin Cases 2: 565-568.
11. Baumann S, Huseynov A, Goranova D, Faust M, Behnes M, et al. (2014) Takotsubo cardiomyopathy after systemic consolidation therapy with high-dose intravenous cytarabine in a patient with acute myeloid leukemia. Oncol Res Treat 37: 487-90.
12. Dombret H, Gardin C (2009) An old AML drug revisited. N Engl J Med 361: 1301-1303.
13. Devillier R, Bertoli S, Prebet T, Huguet F, Etienne A, et al. (2015) Comparison of 60 or 90 mg/m² of daunorubicin in induction therapy for acute myeloid leukemia with intermediate or unfavorable cytogenetics. American journal of hematology 90: E29-E30.

14. Prebet T, Bertoli S, Delaunay J, Pigneux A, Delabesse E, et al. (2014) Anthracycline dose intensification improves molecular response and outcome of patients treated for core binding factor acute myeloid leukemia. Haematologica 99: e185-e187.

15. O'Donnell MR TM, Abboud CN, Altman JK, Applebaum FR (2015) Nccn clinical practice guidelines in oncology acute myeloid leukemia (20th edn), National Comprehensive Cancer Network, Rockledge, PA, USA.

16. Yezefski T, Xie H, Walter R, Pagel J, Becker PS, et al. (2015) Value of routine ‘day 14’ marrow exam in newly diagnosed AML. Leukemia 29: 247-249.

17. Armenian SH, Sun CL, Shannon T, Mills G, Francisco L, et al. (2011) Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. Blood 118: 6023-6029.

18. Armenian SH, Sun CL, Francisco L, Steinberger J, Kurian S, et al. (2008) Late congestive heart failure after hematopoietic cell transplantation. J Clin Oncol 26: 5537-5543.