Availability of all-trans retinoic acid and support systems for management of acute promyelocytic leukemia in Michigan and Louisiana, USA

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Abstract

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia with high induction mortality in the general population despite evidence of high cure rates in the clinical trials. Aggressive supportive care is essential for ideal management of these patients. We conducted a survey to collect data on these important issues required for successful treatment/outcome of APL patients from two states (Michigan and Louisiana) due to their low one-year survival rate among the Surveillance, Epidemiology, and End Results registries. All eligible hospitals (253) were obtained from the Data Medicare online directory. Availability of ATRA, formulary process to obtain it, blood back availability and established treatment protocols for the management of APL patients were queried. Since most of the hospitals surveyed do not have a treatment protocol, we believe that outcome could be improved if a standardized and simplified set of treatment and supportive care guidelines are developed for all hospitals treating APL.

Introduction

The early death (ED) rates associated with acute promyelocytic leukemia (APL) are attributable to differentiation syndrome (DS), infection; however, the most apparent is bleeding due to disseminated intravascular coagulation (DIC). Recently conducted APL clinical trials are exciting as treatment with targeted drugs on a protocol has resulted in cure rates in excess of 90%.[1,2] It is estimated that upwards of 30% of patients in the general population die within 30 days of diagnosis.[3-7] Furthermore, early initiation of all-trans retinoic acid (ATRA), along with aggressive transfusions and supportive care result in decreasing ED. In the APL community the availability of ATRA in leukemia treating hospitals continues to be a concern. We conducted a survey of all APL treatment centers in two US states; Michigan and Louisiana with emphasis on availability of ATRA and other supportive systems to successfully treat APL.

Materials and Methods

Using Surveillance, Epidemiology, and End Results (SEER) registry data, we identified the states of Michigan (population: 9.923 million) and Louisiana (population: 4.671 million) due to their low one-year APL survival rate. All eligible hospitals (132 – Michigan; 121 – Louisiana) were obtained from the Data Medicare online directory (https://data.medicare.gov/). Each hospital was contacted and non-APL treatment facilities were excluded. 23 APL treatment centers (14 Michigan; 9 Louisiana) were contacted by telephone and a survey of seven questions (Table 1) was conducted with pharmacy staff, nurses, hospital administrators, and physicians (hematologists/oncologists). In order to ensure the integrity and consistency of the responses, each treatment facility was contacted three times.

Results

ATRA was available on formulary or in stock at 6 of the 23 hospitals. 4 of the 6 hospitals with ATRA availability were affiliated with a school of medicine (SOM). For 17 of 23 hospitals that did not have ATRA, when asked about the viability of obtaining the drug, these were the responses. i) Could be available within one to two days – 3/17; ii) Needs approval of Pharmacy and Therapeutics Committee – 7/17; iii) Could be available within two weeks – 3/17; iv) Could not give an exact timeline – 4/17. Only 7 of the 17 hospitals were willing to answer a follow-up question about the lack of ATRA. The most common answers were that the pharmacist was unfamiliar with the drug (5 hospitals) or there had not been a recent request (2 hospitals). The remaining 10 hospitals stated that either they were not at liberty to answer the question (6 hospitals) or that they could not give an accurate answer (4 hospitals).

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Regarding availability of a written protocol, 5 of 23 hospitals stated they follow a protocol for treating APL. Of the 5 hospitals, only 1 was not affiliated with a SOM. Additionally, of the 5 hospitals with a protocol, 3 (2 SOMs) have their own written protocol and 2 (1 SOM) follow the National Comprehensive Cancer Network (NCCN) guidelines. For the 18 hospitals that did not have a protocol nor followed the NCCN guidelines, most of them believed that treatment had to be expedited and tailored to the patient's age, blood counts, and other health issues (Figure 1). All APL treating hospitals had trained physicians and a blood bank with the capability to meet transfusion requirements.

Discussion and Conclusions

Upon first suspicion of APL, standard protocol mandates the initiation of ATRA even prior to confirmation of diagnosis. This is done due to the drug's ability to reverse DIC. Altman et al showed delayed administration of ATRA contributes to early hemorrhagic deaths.[8] More than 70% of hospitals in Michigan and Louisiana did not have ATRA in stock or on the formulary that could potentially delay treatment and contribute to poor outcomes. Although our study does not represent a majority of APL treatment centers within the United States, it

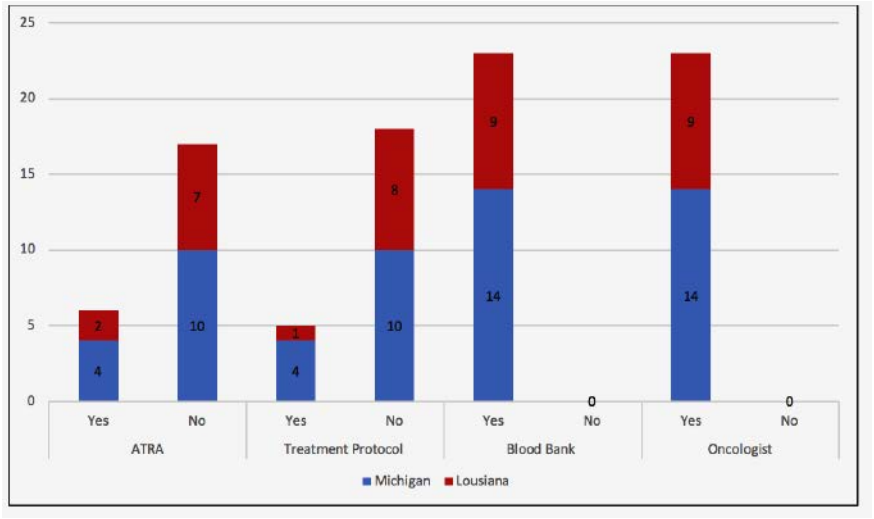

Figure 1. The availability of all-trans retinoic acid (ATRA), a treatment protocol, blood bank, and staff hematologist/oncologist among 23 acute promyelocytic leukemia treatment facilities in Michigan and Louisiana (USA).

Table 1. The survey questions for each of the 23 acute promyelocytic leukemia treatment centers.

Questions
1. Do you have ATRA on formulary?
2. Do you have ATRA in stock?
3. If not on formulary, could you order it?
4. If ordered, how soon would you receive it?
5. Is there a hematologist on staff?
6. Do you have a blood bank?
7. Do you have a treatment protocol?

does suggest a need for evaluation of treatment facilities to ensure ready access to this life saving drug.

In APL clinical trials, patients are treated with strict adherence to supportive care guidelines that result in excellent outcomes.[1,9] The PETHEMA group used meticulous supportive care guidelines on a protocol to manage their patients.[10,11] But such written guidelines may not be available in community hospitals as has been shown by our survey leading to non-standardized management of patients. The vast majority of centers surveyed did not have a written treatment algorithm. Given the rarity of the disease (1000 cases per year in the US), oncologists/hematologists infrequently see an APL patient. While elaborate published guidelines are available, they may be too cumbersome and impractical to implement given the urgency.[12] The Latin American experience showed that implementation of standard guidelines improves the outcome.[13] In addition while the NCCN guidelines have supportive care recommendations, they are not thorough enough and leave too much room for doubt. A concise treatment algorithm would help to improve outcomes and provide uniformity in drug usage as well as supportive care.

The hypothesis going into the survey was that both the availability of ATRA and a written supportive care algorithm would be much higher in the US given our sophisticated health care system. However, we were surprised the data showed results that were exactly opposite to our expectations. The hope of this study is that it serves as a potential catalyst towards creating awareness of the problem of ED, ready availability of ATRA, and written guidelines in order to decrease induction deaths. ED is the most common cause of treatment failure in APL. We believe that in order to reduce ED rate in APL, considerable effort should be made to increase awareness in leukemia centers regarding prompt availability of ATRA and encourage the use of standardized guidelines.

References

1. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013;369:111-21.
2. Iland HJ, Bradstock K, Supple SG, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120:1570-80.
3. Jacomo RH, Melo RA, Souto FR, et al. Clinical features and outcomes of 134 Brazilians with acute promyelocytic leukemia who received ATRA and anthracyclines. Haematologica 2007;92:1431-2.
4. Lehmann S, Ravn A, Carlsson L, et al. Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the Swedish Adult Acute Leukemia Registry. Leukemia 2011;25:1128-34.
5. Park JH, Qiao B, Panageas KS, et al. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. Blood 2011;118:1248-54.
6. McClellan JS, Kohrt HE, Coutre S, et al. Treatment advances have not improved the early death rate in acute promyelocytic leukemia. Haematologica 2012;97:133-6.
7. Jillella AP, Kolhe RB, Natrajan K, Kota V. A successful model to decrease early deaths in acute promyelocytic leukemia (APL) through the use of a simplified algorithm and expert support. J Clin Oncol 2014;32.
8. Altman JK, Rademaker A, Cull E, et al. Administration of ATRA to newly diagnosed patients with acute promyelocytic leukemia is delayed contributing to early hemorrhagic death. Leukemia Res 2013;37:1004-9.
9. Pagnano KB, Rego EM, Rohr S, et al. Guidelines on the diagnosis and treatment for acute promyelocytic leukemia: Associacao Brasileira de Hematologia, Hemoterapia e Terapia Celular Guidelines Project: Associacao Medica Brasileira - 2013. Rev Bras Hematol Hemoter 2014;36:71-92.
10. de la Serna J, Montesinos P, Vellenga E, et al. Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. Blood 2008;111:3395-402.
11. Sanz MA, Martin G, Gonzalez M, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. Blood 2004;103:1237-43.
12. Sanz MA, Grimwade D, Tallman MS, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European Leukemia Net. Blood 2009;113:1875-91.
13. Rego EM, Kim HT, Ruiz-Arguelles GJ, et al. Improving acute promyelocytic leukemia (APL) outcome in developing countries through networking, results of the International Consortium on APL. Blood 2013;121:1935-43.