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Management of chronic myeloid leukemia in the setting of pregnancy: when is leukocytapheresis appropriate? A case report and review of the literature

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Abstract

BACKGROUND: Chronic myeloid leukemia (CML) is a common hematologic malignancy; however, its occurrence during pregnancy is unusual due to its low prevalence in females of childbearing age. There are conflicting reports of how to best manage CML in pregnancy, particularly in the setting of leukocytosis.

CASE REPORT: A 30-year-old female was diagnosed with CML at 18 weeks' estimated gestational age. On initial presentation she reported fatigue, night sweats, and early satiety, and was found to have a white blood cell (WBC) count of $69.3 \times 10^9/L$ and platelet count of $366 \times 10^9/L$. Her disease was managed during pregnancy using interferon- α alone despite persistent leukocytosis.

CONCLUSION: CML may be effectively managed during pregnancy, even in the setting of leukocytosis, without the application of leukocytapheresis. Management relies not only upon the coordination of drug therapy and fetal monitoring, but requires close communication between multiple medical disciplines. Leukocytapheresis has been safely performed during pregnancy and may be a suitable adjunct management strategy in pregnant patients diagnosed with CML with specific clinical presentations, such as hyperleukocytosis (WBC count $> 150 \times 10^9/L$) and/or symptomatic leukostasis.

Chronic myeloid leukemia (CML) is one of the most common hematologic malignancies of adulthood; however, its occurrence during pregnancy is relatively anomalous due to its low prevalence in females of childbearing age. As such, there are conflicting strategies as to how to manage CML during pregnancy. The mainstay of CML therapy is tyrosine kinase inhibitors (TKIs). However, the use of TKIs in pregnancy, dasatinib in particular (and to a lesser degree imatinib), is not recommended due to the association with birth defects and

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CONFLICT OF INTEREST

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adverse pregnancy outcomes.¹ Although large-scale studies are lacking, there is adequate evidence to suggest that interferon- α (IFN- α) is safe in pregnancy, particularly if initiated during the second and third trimesters.^{2,3} However, it must be noted that IFN- α is a second-line therapy for the treatment of CML and is not without significant side effects.

There are several case reports advocating for management of CML in pregnancy through utilization of therapeutic leukocytapheresis, not only in the setting of symptomatic leukostasis, but also prophylactically in the setting of hyperleukocytosis as means of preventing potential placental insufficiency and intrauterine growth restriction.⁴⁻¹⁵ The latter is particularly indicated for women who are unwilling and/or unable to tolerate other forms of therapy. Of note, these indications are not listed in the current American Society for Apheresis guidelines.¹⁶ Furthermore, while leukocytapheresis is useful for amelioration of symptoms and potentially for the prevention of fetal complications associated with placental insufficiency, it plays no role in the long-term or curative treatment of CML.¹⁷ Given this information, we will review a case of a patient with CML who presented during pregnancy and explore her course, treatment, and outcome, with the aim of increasing understanding of management of this disease.

CASE REPORT

A 30-year-old female with a past medical history significant for obesity and severe depression was referred to our institution's Fetal Medicine service at 16 weeks' estimated gestational age (EGA) for evaluation of leukocytosis and presumed CML. At initial presentation, she reported fatigue, night sweats, and early satiety (to a more severe degree than experienced during two prior pregnancies). Subsequent laboratory analysis revealed the following: WBC count, $69.3 \times 10^9/L$; hemoglobin, 10.5 g/dL; hematocrit, 34%; mean corpuscular volume, 85 fL; red blood cell distribution width, 19.6%; and platelet (PLT) count, $304 \times 10^9/L$. The WBC differential demonstrated 64% segmented neutrophils, 10% bands, 3% lymphocytes, 3% monocytes, 1% eosinophils, 3% basophils, 6% metamyelocytes, 3% myelocytes, 6% progranulocytes, 1% atypical lymphocytes, and no blasts. Peripheral blood reverse transcription polymerase chain reaction was positive for the p210 BCR/ABL fusion transcript, and fluorescence in situ hybridization analysis detected the BCR/ABL fusion gene¹⁸⁻²¹ product in 92.5% of cells. The patient was stratified as having low risk disease by the Sokal score (based on age [30 years], spleen size [2 cm below the left costal margin], peripheral blood blast count [0%], and PLT count [$304 \times 10^9/L$]). The patient was extensively advised as to the potential benefits of initiating therapy with a TKI (i.e., the high likelihood of rapidly achieving hematologic remission), as well as the potential risks associated with the use of TKIs in pregnancy.^{1,18-21} The patient refused termination of pregnancy and elected not to initiate TKI therapy. The patient was further advised as to the dangers of untreated CML, and the risk associated with the progression to blast crisis. She was further advised regarding the risks and benefits of IFN- α therapy, which is reported to be safe for use in pregnancy and has been associated with both cytogenetic remissions and delayed transformation to blast crisis.^{1-3,22} At that time the patient elected to forego medical treatment of CML.

Unfortunately, the patient's WBC count increased steadily throughout the second trimester. At 21 weeks' EGA, when it reached $109 \times 10^9/L$, the hematology/oncology, obstetric, and transfusion medicine services considered the appropriateness of leukocytapheresis for the management of her leukocytosis. It has been previously suggested that $100 \times 10^9/L$ may be utilized as a threshold for the application of leukocytapheresis to prevent adverse fetal outcomes in the setting of CML in pregnancy.^{1,23} It was decided that the substantial risks inherent to this procedure (hypotension, fluid shift [potentially leading to decreased placental blood flow], citrate toxicity, thrombocytopenia, hemorrhage, infection, and thrombosis) outweighed the potential benefits and, thus, were not acceptable for treatment of a patient lacking specific symptoms related to leukostasis. Further, it was decided that the patient would be better served by initiating therapy targeted toward treating her underlying disease. The consulting teams advised the patient to proceed with IFN- α reserving leukocytapheresis should she be intolerant to the medication; develop symptomatic leukostasis; or show signs or symptoms of placental insufficiency, intrauterine growth restriction, or fetal distress.

The patient initiated treatment with IFN- α (3 million units, three times weekly) at 25 weeks' EGA (WBC count, $116 \times 10^9/L$; PLT count, $414 \times 10^9/L$). This dose was increased to 5 million units, three times weekly, at 27 weeks' EGA due to persistent leukocytosis (WBC count, $132 \times 10^9/L$; PLT count, $458 \times 10^9/L$). Subsequently, her WBC count marginally declined, stabilizing in the third trimester (WBC count, $82 \times 10^9/L$ at delivery at 37 weeks and 4 days [Fig. 1]). She delivered a 3020-g male infant (Apgar scores 1 and 7) via repeat C-section necessitated by premature rupture of membranes and nonreassuring fetal heart tones. The neonate was admitted to the intensive care unit for respiratory distress and bradycardia at birth, although his symptoms rapidly resolved and he was discharged home on Day 3 of life. No congenital anomalies were observed. Microscopic examination of the placenta was significant for acute subchorionitis and chorionic vasculitis, although no infarcts or ischemic changes were noted.

After delivery, the patient received hydroxyurea (500 mg, twice daily) with the plan to initiate therapy with a TKI at her next follow-up appointment. She initially demonstrated a good response to therapy with hydroxyurea alone. Unfortunately, her peripheral blood analysis 2 weeks postdelivery was significant for 32% blasts (WBC count, $10.2 \times 10^9/L$), and a marrow biopsy confirmed the diagnosis of CML in myeloid blast crisis. The patient has not been able to achieve remission despite aggressive medical therapy (15 months after diagnosis and 9 months after progression to blast crisis). She is currently not a candidate for hematopoietic progenitor cell transplantation and has been referred to hospice care.

DISCUSSION

The diagnosis of CML during pregnancy is an uncommon occurrence, and there are no evidence-based guidelines outlining optimal medical therapy. Ultimately, therapy will be patient-specific and interdisciplinary in nature. There are multiple variables that should be considered when approaching the care of a pregnant patient with CML.

The utilization of TKIs as targeted molecular therapy for the treatment of CML has revolutionized treatment of this disease. TKIs have been shown to dramatically increase long-term survival. In fact, it has been demonstrated that patients who demonstrate a major molecular response within 2 years of treatment have survival rates equivalent to the general population. However, TKIs have been associated with teratogenic effects (likely due to an off-target inhibition of tyrosine kinases crucial for fetal development, such as c-kit or PDGFR) and are likely unsafe for use during pregnancy.¹ Animal studies examining the effects of imatinib, dasatinib, nilotinib, bosutinib, and ponatinib all demonstrated fetal toxicity and malformations at concentrations equivalent to, or lower than, therapeutic concentrations.¹ Pye and colleagues²¹ conducted a retrospective international study of imatinib use during pregnancy demonstrating an association with renal agenesis, exophthalmos, hemivertebrae, hypospadias, and other congenital anomalies. Further evidence was published by Abruzzese and coworkers¹⁸ who reported that imatinib use in the first trimester was associated with spontaneous abortion and congenital malformations. Additionally, there are case reports of adverse outcomes associated with the use of both dasatinib and nilotinib.^{19,20} However, more recently it has been suggested that TKIs may be safe for use in the second or third trimester of pregnancy. Burwick and colleagues²⁴ recently reported treatment of CML in pregnancy with imatinib initiated at the end of the second trimester, with no adverse outcome, despite high concentrations of imatinib being demonstrated in the neonate's urine. Unfortunately, large-scale clinical studies confirming the safety of TKIs later in pregnancy are lacking, and there is a paucity of data regarding the use of bosutinib and ponatinib in that setting. Currently, the standard of care remains that TKIs should not be used during pregnancy, particularly during the first trimester.

Interferon- α is believed to be safe and effective in pregnancy, particularly in the second and third trimesters.¹ It has no known effects on DNA synthesis, and it has been shown to have little transplacental transfer (likely a result of its high molecular weight).²² There were no congenital malformations reported in two separate case series examining the outcomes of patients treated with IFN- α during pregnancy.^{2,3} Further, there are multiple case studies reporting good outcomes for patients who initiated therapy during pregnancy.^{11,15,25,26} However, IFN- α is known to have significant side effects, which many patients are unable to tolerate.^{1,11} Regardless, treatment with IFN- α is likely the best option for management of CML during the second and third trimesters of pregnancy, as it appears to have little impact on pregnancy outcome and fetal development while actively treating maternal disease.

Leukocytapheresis is not an approved, or indicated, procedure for the treatment of CML during pregnancy by the most recent American Society for Apheresis Guidelines on the use of therapeutic apheresis.¹⁶ In addition to being time-consuming and costly and having no direct effect on disease pathogenesis, the procedure itself is not without significant risks. It is known to be associated with infection, bleeding, and thrombosis (of particular concern given that both pregnancy and malignancy are hypercoagulable states). Given that leukocytapheresis requires vascular access (and the potential for multiple procedures if utilized in this clinical setting), a patient either would require the establishment of semipermanent vascular access or would need to be accessed on multiple occasions, placing the patient at increased risk for infection, bleeding, and thrombosis. Additionally, the performance of leukocytapheresis inherently involves fluid shifts and, not infrequently, can

precipitate hemodynamic compromise, which would threaten placental and fetal perfusion. Furthermore, the procedure can exacerbate hypocalcemia and anemia, both of which are common in pregnancy.¹³

Despite these known risks, there are several groups who have proposed leukocytapheresis for management of CML in pregnancy for hyperleukocytosis, symptomatic leukostasis, and/or prophylaxis.^{4,9-15} In fact, there are multiple case reports of leukocytapheresis being employed safely and effectively in this population, with no adverse outcomes reported for either the mother or the fetus for the duration of the pregnancy (Table 1). However, it is unclear at what threshold one should perform this apheresis procedure to treat leukocytosis in an asymptomatic pregnant patient with CML. In a review published by Palani and colleagues¹ in 2015, a threshold of a WBC count of $100 \times 10^9/L$ and a PLT count of $500 \times 10^9/L$ was proposed (with concurrent initiation of aspirin and low-molecular-weight heparin for the latter). In a recent review by Abruzzese and colleagues,²⁷ a more liberal threshold of 100×10^9 to $150 \times 10^9/L$ and 500×10^9 to $1000 \times 10^9/L$, respectively, was suggested. The experience with the patient reported here supports a more liberal threshold for the application of leukocytapheresis in patients not exhibiting symptomatic leukostasis.

In conclusion, the diagnosis of CML in pregnancy is relatively uncommon, and management is currently complicated by lack of evidence-based guidelines. Ultimately, the optimal management strategy for such patients should be individualized as well as patient- and situation-specific. Physicians involved will not only need to evaluate data from multiple cases studies, but additionally seek out expert opinion and synthesize a treatment plan in accordance with the needs and wishes of the patient. Patients diagnosed with CML during pregnancy should be advised of the potential risks associated with treatment delay. While pregnancy in and of itself does not affect the course of CML, there is a risk for maternal disease progression if CML remains untreated for the duration of pregnancy. Unfortunately, treatment of CML during pregnancy is complicated due to the teratogenic nature of TKIs. Patients must be counseled regarding all available options, including the possibility of pregnancy termination. Ultimately, if the patient wishes to maintain her pregnancy, multiple disciplines must coordinate to provide optimal care, and the mother and fetus must be closely monitored so that care may be initiated promptly when indicated.

ABBREVIATIONS:

CML	chronic myeloid leukemia
EGA	estimated gestational age
TKI(s)	tyrosine kinase inhibitor(s)

REFERENCES

1. Palani R, Milojkovic D, Apperley JF. Managing pregnancy in chronic myeloid leukaemia. *Ann Hematol* 2015;94 Suppl 2: S167–76. [PubMed: 25814083]
2. Hiratsuka M, Minakami H, Koshizuka S, et al. Administration of interferon-alpha during pregnancy: effects on fetus. *J Perinat Med* 2000;28:372–6. [PubMed: 11125927]

3. Vantroyen B, Vanstraelen D. Management of essential thrombocythemia during pregnancy with aspirin, interferon alpha-2a and no treatment. A comparative analysis of the literature. *Acta Haematol* 2002;107:158–69. [PubMed: 11978937]
4. Ali R, Ozkalemkas F, Ozkocaman V, et al. Successful pregnancy and delivery in a patient with chronic myelogenous leukemia (CML), and management of CML with leukapheresis during pregnancy: a case report and review of the literature. *Jpn J Clin Oncol* 2004;34:215–7. [PubMed: 15121759]
5. Bazarbashi MS, Smith MR, Karanes C, et al. Successful management of Ph chromosome chronic myelogenous leukemia with leukapheresis during pregnancy. *Am J Hematol* 1991;38: 235–7. [PubMed: 1951325]
6. Bell R, Sullivan JR, Hurley TH, et al. Some uses of the continuous flow blood separator in the myeloproliferative syndrome. *Aust N Z J Med* 1978;8:433–5. [PubMed: 282861]
7. Broccia G, Casula P, Andria M. Chronic myelocytic leukemia in pregnancy: report of a case treated with leukapheresis. *Tumori* 1984;70:371–4. [PubMed: 6591604]
8. Caplan SN, Coco FV, Berkman EM. Management of chronic myelocytic leukemia in pregnancy by cell pheresis. *Transfusion* 1978;18:120–4. [PubMed: 272800]
9. Fitzgerald D, Rowe JM, Heal J. Leukapheresis for control of chronic myelogenous leukemia during pregnancy. *Am J Hematol* 1986;22:213–8. [PubMed: 3458363]
10. Fitzgerald JM, McCann SR. The combination of hydroxyurea and leucapheresis in the treatment of chronic myeloid leukaemia in pregnancy. *Clin Lab Haematol* 1993; 15:63–5. [PubMed: 8472499]
11. Galera P, Haynes S, Sulmasy P et al. Physiological measurements corroborate symptomatic improvement after therapeutic leukapheresis in a pregnant woman with chronic myelogenous leukemia. *J Clin Apher* 2016;31: 393–7. [PubMed: 26053950]
12. Klaasen R, de Jong P Wijermans PW. Successful management of chronic myeloid leukaemia with leucapheresis during a twin pregnancy. *Neth J Med* 2007;65:147–9. [PubMed: 17452764]
13. Morris A, McMullin MF, Benson G. Management of newly diagnosed chronic myeloid leukaemia during a twin pregnancy using leucapheresis: case report and review of the literature. *Transfus Apher Sci* 2015;52:199–203. [PubMed: 25634790]
14. Strobl FJ, Voelkerding KV, Smith EP. Management of chronic myeloid leukemia during pregnancy with leukapheresis. *J Clin Apher* 1999;14:42–4. [PubMed: 10355663]
15. Yellu M, Pinkard S, Ghose A, et al. CML in pregnancy: a case report using leukapheresis and literature review. *Transfus Apher Sci* 2015;53:289–92. [PubMed: 26231323]
16. Schwartz J, Winters JL, Padmanabhan A, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. *J Clin Apher* 2013;28:145–284. [PubMed: 23868759]
17. Pham HP, Schwartz J. How we approach a patient with symptoms of leukostasis requiring emergent leukocytapheresis. *Transfusion* 2015;55:2306–11; quiz 2305. [PubMed: 26267387]
18. Abruzzese E, Trawinska MM, Perrotti AP, et al. Tyrosine kinase inhibitors and pregnancy. *Mediterr J Hematol Infect Dis* 2014;6:e2014028. [PubMed: 24804001]
19. Berveiller P, Andreoli A, Mir O, et al. A dramatic fetal outcome following transplacental transfer of dasatinib. *Anticancer Drugs* 2012;23:754–7. [PubMed: 22421368]
20. Etienne G, Milpied B, Rea D, et al. [Guidelines for the management of nilotinib (Tasigna)-induced side effects in chronic myelogenous leukemia: recommendations of French Intergroup of CML (Fi-LMC group)]. *Bull Cancer* 2010;97: 997–1009. [PubMed: 20529767]
21. Pye SM, Cortes J, Ault P et al. The effects of imatinib on pregnancy outcome. *Blood* 2008;111:5505–8. [PubMed: 18322153]
22. Baer MR, Ozer H, Foon KA. Interferon-alpha therapy during pregnancy in chronic myelogenous leukaemia and hairy cell leukaemia. *Br J Haematol* 1992;81:167–9. [PubMed: 1643013]
23. Milojkovic D, Apperley JF. How I treat leukemia during pregnancy. *Blood* 2014;123:974–84. [PubMed: 24269956]
24. Burwick RM, Kuo K, Brewer D, et al. Maternal, fetal, and neonatal imatinib levels with treatment of chronic myeloid leukemia in pregnancy. *Obstet Gynecol* 2017;129: 831–4. [PubMed: 28383372]

25. Regierer AC, Schulz CO, Kuehnhardt D, et al. Interferon-alpha therapy for chronic myeloid leukemia during pregnancy. *Am J Hematol* 2006;81:149–50.
26. Trotter JF, Zygmunt AJ. Conception and pregnancy during interferon-alpha therapy for chronic hepatitis C. *J Clin Gastroenterol* 2001;32:76–8. [PubMed: 11154177]
27. Abruzzese E, Trawinska MM, de Fabritiis P, et al. Management of pregnant chronic myeloid leukemia patients. *Expert Rev Hematol* 2016;9:781–91. [PubMed: 27352939]

Fig. 1.
Patient's WBC (discontinuous line) and PLT counts (solid line) for the duration of pregnancy.

TABLE 1.
Previously reported cases of management of CML in pregnancy with leukocytapheresis

Authors	Age (weeks) [*]	EGA [*]	WBCs; PLTs [†] (×10 ⁹ /L)	Symptoms	Leuko [‡]	Indication	Additional therapy (EGA) [§]	EGA; WBCs (×10 ⁹ /L); BW (kg)
Caplan et al. ⁸	23	10	350; 1790	None	5	NA	Radiation (16), busulfan (21)	37; NA; NA
Bell et al. ⁶	27	29	100; NA	Malaise	2	NA	None	NA; 51; NA
Fitzgerald et al. ⁹	29	11	252; 600	Fatigue	17	WBCs > 100	None	37; ~60; 3.05
Broccia et al. ⁷	24	15	144; 470	None	8 [¶]	NA	None	37; ~40; 2.85
Bazarbashi et al. ⁵	25	29	205; 499	None	11	WBCs > 100	None	38; 11; 3.41
Fitzgerald and McCann ¹⁰	26	Pre	170; 420	None	13	WBCs > 200	HYD (~20)	Term; NA; 3.4
Strobl et al. ¹⁴	39	13	242; 600	None	20	NA	None	38; ~25; 2.64
Ali et al. ⁴	26	12	131; 944	None	15	WBCs > 100	None	36; 54; 2.8
Klaassen et al. ¹²	36	16	140; 262	Dyspnea	14	WBCs > 100	None	36 (twins); ~50; 2.69 & 2.64
Yellu et al. ¹⁵	37	8	173; 296	None	8	WBCs > 100	IFN-α (8)	35; 107; NA ^{**}
Galera et al. ¹¹	27	10	154; NA	Dyspnea	12	Symptoms	IFN-α (10)	32; 30; 1.76
Morris et al. ¹³	32	11	219; 581	None	7	WBCs > 100	None	37 (twins); ~75; 2.2 & 1.9

^{*} At diagnosis.

[†] At initiation of apheresis.

[‡] Total number of procedures.

[§] EGA at initiation of additional therapy.

^{||} At delivery (all described as “healthy” with no congenital anomalies).

[¶] Procedures performed weekly.

^{**} Partial abruption with significant postpartum hemorrhage.

Leuko=leukocytapheresis; BW=birthweight; NA=not available; HYD=hydroxyurea.