Secondary Acute Myeloid Leukemia after Polycythemia Vera: A Case Report

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Abstract: Secondary acute myeloid leukemia (AML) can be found as the complication of polycythemia vera (PV) itself or the association with chemotherapy particularly hydroxyurea (HU). Herein we report a case of 52-year old Thai woman who was diagnosed as PV based on the combination of the erythrocytosis, leukocytosis, thrombocytosis, huge splenomegaly and normal oxygen saturation. She has been treated with continual HU with occasional phlebotomy for nine years. The dose of HU has been adjusted according to the white blood cell count. Finally she develops chronic fever, weight loss, anemia, marked leukocytosis with predominant blasts in the peripheral blood and recurrent huge splenomegaly. The definite diagnosis of secondary AML after PV can be made by the bone marrow immunophenotyping and positive JAK2 mutation. She is treated with the combination of cytosine arabinoside and idarubicin regimen and she can tolerate it well. With this case report, the association of the incident of AML after PV and HU therapy is discussed.

บทคัดย่อ: **มะเร็งเม็ดเลือดขาวเฉียบพลันไมอีลอยด์ชนิดทุติยภูมิหลัง polycythemia vera: รายงานผู้ป่วย 1 ราย**
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มะเร็งเม็ดเลือดขาวเฉียบพลันชนิดทุติยภูมิ สามารถเกิดขึ้นเป็นภาวะแทรกซ้อนของโรค polycythemia vera (PV) เอง หรืออาจจะเกี่ยวข้องกับการได้รับยาเคมีบำบัดก็ได้โดยเฉพาะ hydroxyurea (HU) ในรายงานนี้เป็นผู้ป่วยหญิงไทย อายุ 52 ปี ซึ่งป่วยเป็น PV ก่อน โดยให้การวินิจฉัยได้จากการที่ผู้ป่วยมีเม็ดเลือดแดง เม็ดเลือดขาว และเกล็ดเลือดมากเกินไป ร่วมกับการมีม้ามที่โตมาก และความอิ่มตัวของออกซิเจนปกติ ได้รับการรักษาด้วยยา HU อย่างสม่ำเสมอ ร่วมกับการเจาะเลือดออกเป็นครั้งคราว เป็นเวลานาน 9 ปี ขนาดของยา HU ปรับขึ้นลงตามปริมาณเม็ดเลือดขาว แต่ในที่สุดผู้ป่วยก็มีไข้เรื้อรังร่วมกับน้ำหนักลด เลือดจางชัดเจน เม็ดเลือดขาวเพิ่มขึ้นมากโดยเฉพาะเม็ดเลือดขาวตัวอ่อนเพิ่มอย่างเด่นชัด ม้ามก็กลับมาโตขึ้นมากอีกครั้งหนึ่ง เมื่อตรวจไขกระดูกด้วยวิธี immunophenotyping และตรวจเลือดพบยีน JAK2 mutation จึงให้การวินิจฉัยที่แน่นอนว่าเป็นมะเร็งเม็ดเลือดขาวเฉียบพลัน ชนิดทุติยภูมิตามหลัง PV จึงให้การรักษาด้วยยาเคมีบำบัดสูตร cytosine arabinoside ร่วมกับ idarubicin ผู้ป่วยทนยาได้ดี จากการปรากฏของผู้ป่วยรายนี้ จึงได้ทบทวนความสัมพันธ์ระหว่างการเกิด AML ที่เกิดตามหลัง PV กับการใช้ HU

Introduction

Polycythemia vera (PV) is the most common disease ofthe myeloproliferativeneoplasia, the abnormal clonal proliferation of the hematopoietic stem cells, characterized by erythrocytosis with JAK2 mutation and noBCR-ABL genes[1]. It always occurs in the old age group, the median age is 61 years. The patients with PV may or may not have splenomegaly, plethora, pruritus or erythromelalgia. It usually runs chronic course, the median survival is 14.1 years that is significantly worse than that of the age- and sex-matched population. If follow-up is long enough, some patients transform toacute myeloid leukemia, the most common cause of death, or to myelofibrosis[2].

To transform to secondary acute leukemia, some authors find no association between chemo-therapy and the incidence of leukemia trans-formation[2]. On the other hand, some authors find that the patients with PV who were treated with HU has more leukemic transformation than the group treated with phlebotomy alone until they recommend not to use HU in the young age group[3]. Besides HU, radioactive phosphorus, chlorambucilare also associated with the higher prevalence of secondary acute leukemia[4]. Herein we report one case of PV who transforms to secondary acute myeloid leukemia (AML) after receiving HU for PV for nine years.

Case Report

A 52-year-old Thai woman was referred to the hematologist because of chronic low-grade fever without chill for two months. She had no organ-specific symptom. She lost her weight for 8 kg. Her blood tested showed Hb 6.0 g%, WBC 61,000/mm^3, platelet 358,000/mm^3, N 2 %, blast 98 %, NRBC 4 % of WBC. And her provisional diagnosis was secon-dary acute leukemia after PV.

Nine years ago, the diagnosis of PV had been established during check-up because she was found to have the combination of Hb 16.6 g%, WBC 13,470/mm^3, platelet 455,000/mm^3, huge splenomegaly, normal oxygen saturation, no cyanotic heart or chronic lung diseases[5]. And she had been treated with occasional phlebotomy and regular hydroxyurea (HU), ASA. During long term follow-up,

her Hblevels werestill higher than 15.0 g% every visit even if she well continued HU through the very long periodwith dose adjustment according to the fluctuation of the WBC. The size of spleen was slightly decreased.

On admission, she was slim, had mild pallor, generally dark skin. She had temperature of 38.9 degree Celsius, hepatomegaly 4 FB and splenomegaly 5 FB below costal margins, no lymphadenopathy.

The bone marrow showed packed blasts which are compatible withthe diagnosis of AML, CD34+, TdT-, MPO+.

The PCR for JAK2 mutation was positive; flow cytometryshowed an increased abnormal population in dim CD45/low SSC region that comprised approximately 78.0 % of all nucleated cells and expressed MPO/CD34/CD117/HLA-DR /CD11b.CD64/CD19/CD20/CD7/CD3/CD5/ cytoplasmic CD3/cytoplasmic CD79a were negative. Aberrant negative of CD13/CD33 was found. The chromosome study showed 46,XX,inv (3)(q21q26.2)[20].

Others: creatinine 0.7 mg%, uric acid 5.0 mg%, albumin 3.4 g%

The final diagnosis was secondary AML after PV. After supportive treatment with empirical antibiotics and blood transfusion, she was treated with the combination of cytosine arabinosideanddarubicin. She could tolerate the regimen well. One month later, she could not achieve complete remission.

Discussion

Our case was diagnosed as PV based on the criteria of Hb>16.5 g%,WBC >12,000/mm^3, platelet >450,000/mm^3, splenomegaly and normal oxygen saturation, and confirmed by positive JAK2 mutation that is found in 98 % of cases with PV and in half cases of essential thrombocythemia[6]. And then she transforms to AML, the most common secondaryleukemia. It is rare to find acute lymphoblastic leukemia in this situation[7].

The treatment of PV may be phlebotomy alone, chemotherapy including HU, radioactive phosphorus, chlorambucilor the newly come JAK2 inhibitor[8]. Neilsen et al found more AML in the patients who received HU particularly previously treated withbusulphanand did not recommend chemotherapy in the young patients[3]. On contrary, the prospective study including 1,638 patients showed HU alone did not enhance the risk of leukemia in comparison with patients treated with phlebotomy only but more AML was associated with HU withmelphalan, chlorambucil[2], phosphorus 32, pipobroman, busulfanand other factors such as the age of 70 years or more and abnormal chromosome[9]. Someauthors find that HU is associated with a more frequent progression to AML when given before or after alkylating agents orradiophosphorus[10]. However, there is no randomized study powered to assess the relative risk of malignant transformation in HU-treated patients[11].

In a study of chromosome in AML after PV, the chemotherapy group has -5/5q- in 46%, -7/7q- in 31%, numerous translocations in 39% and unidentified markers in 36%. Half of the patients treated with HU alone show -5 or 5q- abnormality. In phlebotomy alone, +8 and +9 is the most frequent findings. And the authors conclude that the type of therapy for PV influences the type of chromosome abnormalities in terminal

AML and the development of leukemia[12].

Conclusion

A 52-year old Thai woman is definitely diagnosed as secondary AML, based on the immunophenotype of the bone marrow and positive JAK2 mutation, nine years after the diagnosis of PV and treatment with hydroxyurea (HU). Although the association between the incident of AML and the use of HU in cases of PV is not firmly documented, avoidance of HU in young patients should be practiced.

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AML and the development of leukemia[12].

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