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 a 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 AM Lafter PV can be made by the bone marrow immunophenotyping and positive JAK2 V617F 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.

Key words: Secondary Acute Myeloid Leukemia, Polycythemia Vera, JAK V617F Mutation

บทคัดย่อ: **มะเร็งเม็ดเลือดขาวเฉียบพลันไมอีลลอยด์ชนิดทุติยภูมิหลัง polycythemia vera: รายงานผู้ป่วย 1 ราย**
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มะเร็งเม็ดเลือดขาวเฉียบพลันชนิดทุติยภูมิสามารถเกิดขึ้นเป็นภาวะแทรกซ้อนของโรค polycythemia vera (PV) เองหรืออาจจะเกี่ยวข้องกับการได้รับยาเคมีบำบัดก็ได้โดยเฉพาะยา hydroxyurea (HU) ในรายงานนี้เป็นผู้ป่วยหญิงไทยอายุ 52 ปี ซึ่งเคยป่วยเป็น PV ก่อนโดยวินิจฉัยได้จากการที่ผู้ป่วยมีเม็ดเลือดแดงเม็ดเลือดขาวและเกล็ดเลือดมากเกินไปร่วมกับการมีม้ามที่โตมากและความอิ่มตัวของอ็อกซิเจนปกติได้รับการรักษาด้วยยา HU อย่างสม่ำเสมอร่วมกับการเจาะเลือดออกเป็นครั้งคราวเป็นเวลานาน 9 ปี ขนาดของยา HU ปรับขึ้นลงตามปริมาณ เม็ดเลือดขาวแต่ในที่สุดผู้ป่วยก็มีไข้เรื้อรังร่วมกับน้ำหนักลดเลือดจางชัดเจนเม็ดเลือดขาวเพิ่มขึ้นมากโดยเฉพาะ เม็ดเลือดขาวตัวอ่อนเพิ่มอย่างเด่นชัด ม้ามก็กลับมาโตขึ้นมากอีกครั้งหนึ่งเมื่อตรวจไขกระดูกด้วยวิธี immuno-phenotyping และตรวจเลือดพบยีน JAK2 V617F mutation จึงให้การวินิจฉัยที่แน่นอนว่าเป็นมะเร็งเม็ดเลือด ขาวเฉียบพลันชนิดทุติยภูมิตามหลัง PV จึงให้การรักษาด้วยยาเคมีบำบัดสูตร cytosine arabinoside ร่วมกับ idarubicin ผู้ป่วยทนยาได้ดีจากการปรากฏของผู้ป่วยรายนี้จึงได้ทบทวนความสัมพันธ์ระหว่างการเกิด AML ที่เกิดตามหลัง PV กับการใช้ HU

คำสำคัญ: มะเร็งเม็ดเลือดขาวเฉียบพลันไมอีลอยด์ชนิดทุติยภูมิ, Polycythemia vera, JAK V617F Mutation

Introduction

Polycythemia vera (PV), is one of the myelo-proliferativeneoplasia, the abnormal clonal prolife-ration of the hematopoietic stem cells, characterized by the erythrocytes is with the presence of JAK2 mutation and no BCR-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 clinically 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 the follow-up is long enough, some patients transform tosecondary acute 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 for a long time 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 mye-loid leukemia (AML) after receiving HU therapy 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 secondary acute leukemia after PV.

Nine years ago, herdiagnosis of PV had been established during check-up because she was found to have the combination of Hb concentration 16.6 g%, WBC 13,470/mm^3, platelet 455,000/mm^3, the huge splenomegaly, normal oxygen saturation, no cyanotic heart or chronic lung diseases[5]. And she had been treated with occasional phlebotomy and regular hy-droxyurea (HU) as well as ASA. During very long term follow-up, her Hb levels were always higher than 15.0 g% every visit even if she well continued HU therapy through the very long periodwith dose adjus-tment according to the fluctuation of the WBC. The size of spleen was slightly decreased. However she had never developed any thrombohemorrhagic symptom.

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, no ecchymosis.

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

The PCR for JAK2V617F mutation was posi-tive; the flow cytometryshowed an increased abnormal population in dim CD45/low SSC region that com-prised 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)(q21q 26.2)[20].

Other blood tests: 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 arabinoside and idarubicin. She could tolerate the regimen well. One month later, instead of the achievement of complete remission, she developed severe sepsis with severe neutropenia and died few days later.

Discussion

Our case wasformerly 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 V617F mutation that is generally found in 98 % of cases with PV and in half cases of essential throm-bo-cythemia[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 with busulphan and finally did not recommend chemo-therapy in the young patients with PV[3]. On contrary, the prospective study including 1,638 patients showed HU alone did not enhance the risk of acute leukemia in comparison with patients treated with phlebotomy only but more AML was associated with HU with melphalan, chlorambucil[2], phosphorus 32, pipobro-man, 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 alkyl ting agents or radio phosphorus[10]. However, there is no randomized studypowered to assess the relative risk of malignant transformation in HU-treated patients[11].

      In a study of chromosome in AML after PV, thechemotherapy 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 are 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]. However the chromosome abnormality in our case wasinv(3)(q21q26.2) that was not consistent with either of both groups. Moreover, the AML with inv(3)(q21q26.2) was distinguished as a distinct entity with usually high platelet count which was quite different from other entities and the poorer prognosis according to the WHO classification[13].

Conclusion

      A 52-year old Thai woman is definitely diag-nosed as secondary AML, based on the immuno-phe-notype of the bone marrow and positive JAK2 V617F mutation, nine years after the diagnosis of PV and treatment with hydroxyurea (HU). Although the association between the incident of secondary AML and the use of HU in cases of PV is not firmly documented, the avoidance of HU therapy in young patients should be practiced.

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