Model Predicting Bone Marrow Infection as a Cause of Cytopenias in HIV Patients

Dechwit Worasayan MD, Dip. Hematology, Dip. Medical Oncology[1]*

[1] Department of Medicine, Chonburi Hospital, Chonburi, Thailand.

* Correspondence to: Dechwit Worasayan, MD. Department of Medicine, Chonburi Hospital, Chonburi, 20000 Thailand. dworasayan@yahoo.com

Abstract

Introduction: Cytopenias are common in HIV patients. They may be caused by multiple mechanisms including occult bone marrow infection (BMI). The objectives of this study were to describe the characteristics and clinical course of HIV patients with cytopenia and to create a predictive model of BMI for those patients in whom a bone marrow examination (BME) is warranted.

Method: Cases of HIV patients with cytopenias who had a BME at Chonburi Hospital from January 2005 to December 2009 were retrospectively reviewed. History of opportunistic infection (OI) and previous drugs taken, as well as patient characteristics such as fever, lymphadenopathy (LN) and hepatosplenomegaly (HS) were recorded. Laboratory result such as complete blood count, CD4 level, alkaline phosphatase (ALP) level and BME findings were obtained from their medical records. Natural history including survival was described. Logistic regression was used to establish a predictive model for decision about risk of BMI.

Result: Forty-three patients, predominately male (60.5%), were included in the study. The mean age of the subjects was 36.8 years (21-66). Most of the patients had symptomatic HIV and mean CD4 level was 67.4 cells/mm^3 (0-604). Tuberculosis (TB) was the most common previous OI at 76.7%. Antiretroviral drugs were being taken by 34.9% of subjects. At the time of BME, 69.8% had fever and 58.3% had LN and/or HS. All the subjects had anemia and 46.5% had a low absolute neutrophil count. The mean ALP level was 271.5 IU/L (43-1173). A BME showing a myeloid:erythoid ratio greater than 3:1 was present in 47.4%. Plasmacytosis was seen in 91.4%, a left shift in the myeloid series in 75%and dysplastic cells in 40.5%. Only 8% had an absence of iron deposits on their BME. All of the stains and cultures for infection were negative. Most of the BME findings (65%) were nonspecific for any definite diagnosis. Of the 15 cases with a definite diagnosis by their pathologic finding, 46.7% had TB; the others were Pneumocystis jirovecii and histoplasmosis. The medial overall survival was 501 days. A concordance finding of LN and HS has a significantly negative impact to the patient's survival. ($p = 0.005$) The predictive model was created.

Conclusion: Cytopenia in an HIV patient is the sign of more advanced disease. Organomegaly was found to be a significantly poor prognostic factor in these cases. Reactive BM and dysplastic features stated as unspecific BM were mostly found. True BMI was less. A predictive model was created to effectively determine suitable cases to have BMI. The limitation of this study was small sample size.

Keywords: model estimation, HIV, bone marrow Infection

สมการทำนายการติดเชื้อในไขกระดูกในผู้ป่วยไวรัสภูมิคุ้มกันบกพร่องที่มีภาวะเม็ดเลือดต่ำร่วมด้วย

เดชวิทย์ วรสายัณห์, พบ., วว. (อายุรศาสตร์โรคเลือด), วว. (อายุรศาสตร์มะเร็งวิทยา)[1]*

[1] กลุ่มงานอายุรกรรม, โรงพยาบาลชลบุรี, ชลบุรี, ประเทศไทย

* ผู้ติดต่อ, อีเมล์: dworasayan@yahoo.com

บทคัดย่อ

บทนำ: ภาวะเม็ดเลือดต่ำเป็นภาวะแทรกซ้อนที่พบได้บ่อยในผู้ป่วยไวรัสภูมิคุ้มกันบกพร่อง (HIV) โดยมีสาเหตุมาจากหลายกลไก การติดเชื้อในไขกระดูกเป็นสาเหตุหนึ่งที่พบได้บ่อย

วิธีการดำเนินการวิจัย: วัตถุประสงค์เพื่อศึกษาลักษณะทางคลินิกของโรค การดำเนินโรค ของผู้ป่วย HIV ที่มีเม็ดเลือดต่ำ และสร้างแบบจำลองเพื่อทำนายการติดเชื้อในไขกระดูก โดยศึกษาย้อนหลังจากเวชระเบียนผู้ป่วยโรค HIV ที่มีภาวะเม็ดเลือดต่ำและได้รับการตรวจไขกระดูกใน รพ.ชลบุรี ตั้งแต่ มกราคม 2548 ถึง ธันวาคม 2552 โดยเก็บข้อมูลประวัติการติดเชื้อฉวยโอกาส ยาที่ได้รับ ลักษณะทางคลินิก เช่น ไข้ ต่อมน้ำเหลืองหรือตับม้ามโต ผลทางห้องปฏิบัติการ เช่น การตรวจนับเม็ดเลือดอย่างสมบูรณ์, ระดับ CD4, ระดับ alkaline phosphatase (ALP) และผลตรวจไขกระดูก รวมทั้งการดำเนินโรคและอัตราการรอดชีวิต โดยใช้การวิเคราะห์ถดถอยโลจิสติกสร้างสมการทำนายความเสี่ยงที่จะมีการติดเชื้อในไขกระดูก

ผลการวิจัย: มีผู้ป่วยในการศึกษา 43 ราย เป็นชายร้อยละ 60.5 อายุเฉลี่ย 36.8 ปี (21-66) โดยมากจะเป็นผู้ป่วยที่มีอาการโรค โดยพบมีระดับ CD4 เฉลี่ย 67.4 cell/mm3 (0-604) วัณโรคเป็นเชื้อฉวยโอกาสที่พบมากที่สุด (76.7%) และร้อยละ 34.9 ได้รับยาต้านไวรัสมาแล้ว ระหว่างการตรวจไขกระดูก ผู้ป่วยมีไข้ ร้อยละ 69.8 มีต่อมน้ำเหลือง และ/หรือ ตับม้ามโตร้อยละ 58.3 ผู้ป่วยทุกรายมีภาวะซีด และมีจำนวนนิวโทรฟิลต่ำ ร้อยละ 46.5 ค่าเฉลี่ยของระดับ ALP เท่ากับ 271.5 IU/L (43-1173) การตรวจไขกระดูกพบว่ามีอัตราส่วนเม็ดเลือดขาวต่อเม็ดเลือดแดงสูงขึ้นในผู้ป่วยร้อยละ 47.4 มีพลาสมาเซลล์สะสม ร้อยละ 91.4 และมีภาวะเม็ดเลือดขาวตัวอ่อนถูกกระตุ้น ร้อยละ 75 ตรวจพบภาวะเม็ดเลือดลักษณะผิดปกติ ร้อยละ 40.5 มีเพียงร้อยละ 8 ที่ไม่มีเหล็กสะสมในไขกระดูก การเพาะเชื้อจากไขกระดูกทั้งหมดให้ผลลบ ผลการตรวจไขกระดูกส่วนใหญ่ไม่จำเพาะ (65%) มีเพียง 15 รายที่สามารถให้การวินิจฉัยได้จากการตรวจทางพยาธิวิทยา โดยพบ TB ร้อยละ 46.7 รองลงมาคือ Pneumocystis jirovecii และ Histoplasmosis ค่ามัธยฐานการรอดชีวิต 501 วัน พบว่าการมีต่อมน้ำเหลือง และ/หรือ ตับม้ามโต มีผลต่อการรอดชีวิต (p = 0.005) และนำมาสร้างสมการประมาณการทำนายสุดท้าย

สรุป: ผู้ป่วย HIV ที่มีเม็ดเลือดต่ำ จะมีระยะโรคที่เป็นมาก การมีต่อมน้ำเหลือง และ/หรือ ตับม้ามโต บ่งบอกถึงการพยากรณ์โรคที่ไม่ดีในผู้ป่วยเหล่านี้ ภาวะไขกระดูกถูกกระตุ้น เม็ดเลือดหน้าตาผิดปกติ พบได้มากจากการตรวจไขกระดูก แต่ไม่ได้บ่งชี้ความผิดปกติแน่ชัด การติดเชื้อในไขกระดูกจริงๆ พบได้เป็นส่วนน้อย นำมาซึ่งการสร้างสมการการทำนายเพื่อหาผู้ป่วยที่เหมาะสมที่จะทำการตรวจไขกระดูกต่อไป ข้อจำกัดคือกลุ่มตัวอย่างมีจำนวนน้อย

คำสำคัญ: สมการทำนาย, ไวรัสภูมิคุ้มกันบกพร่อง, การติดเชื้อในไขกระดูก

Introduction

Cytopenias are common in HIV patients. The etiology can be caused by HIV itself to infect bone marrow (BM) stem cells which disturbs cell differentiation and alter immunity of host cells. It can be induced by the effect of many cytokines to impact the BM microenvironment leading to inappropriate cell well-being. Drugs that are used to prevent opportunistic infection (OI) or even the antiretroviral therapy (ARV) that is used to increase the chances of survival may cause cytopenias through BM suppression or autoimmunity. Concurrent OI can also enhance the negative impact to both BM and peripheral cells as the antecedent factors. OIs can also directly infect BM[1,2]. Anemia is the most frequent complication followed by leucopenia and thrombocytopenia[3]. They can lead to fatal disorders and diminish the quality of life of patients[4] whereas asymptomatic cytopenias have been reported that do not need any treatment[5]. Hematologists are usually justified in correcting this disorder while it has been found that this condition is not detected in most patients through a BM examination (BME)[6,7,8]. The BM diagnosis may show a secondary dysplastic change or unspecific BM that requires no specific treatment except blood replacement. BME is also risky for medical personnel treating such patients and also for those involved in the testing of the specimen. Many patients had poor performance status and expressed fear of this difficult and invasive procedure, and may refuse it. Therefore, it is necessary to be more discriminating when selecting patients in order to avoid a procedure that may be of little value for some patients. The demonstration of OI in BME is the only method which justifies the use of BME. There are no diagnostic criteria for using BME which ensure protection against OIs; therefore, most patients usually have external findings or positive culture concordant with BM infection[9,10]. The finding of BM involved infections (BMI) does not change any drug treatment regimen. Consequently, the value of BME for cytopenias in HIV patients requires further investigation. This study aimed to describe the characteristics of cytopenias in HIV patients and their BME findings. Natural course including survival time and related factors was studied. A predictive model to assist physicians to perform BME in these patients was created.

Material and methods

Patients and study design

This study retrospectively reviewed the medical records of all HIV patients who had a BME to investigate suspected BMI at Chonburi Hospital from January 2005 to December 2009. The diagnosis of hospital subjects was determined using the International Classification of Diseases (ICD), 10th version. HIV infection was coded with B 20-B24 and the ICD 9 clinical modification (ICD-9-CM) as the procedure code for BME as 4131. All subjects were older than 18 years of age. This research was approved by the Ethics Committee of Chonburi hospital.

At the time of BME, history of OIs, drugs used, and hepatitis profiles were reviewed. The presence of fever, lymphadenopathy (LN) and hepatosplenomegaly (HS) were recorded. Complete blood count (CBC), bilirubin, albumin (ALB), alanine transaminase (ALT), alkaline phosphatase (ALP), blood cryptococcal antigen (CRAG), and CD4 level were collected. The BME result and the diagnosis were evaluated for definite diagnosis of BMI finding by pathology and/or staining, HIV-induced secondary dysplasia and other nonspecific abnormalities. Cultures of peripheral blood and BM for fungus and tuberculosis (TB) were also collected. The date of HIV diagnosis and BME were recorded. This report used the national census to establish the patients' date of death. Each of preceding factors were obtained to include in the log rank test.

The exclusion criterion was BME for hematological indication such as to establish the stage of their cancer.

Statistical methods

Means and standard deviations were determined for the continuous variations.

Frequencies and percentages were calculated for the categorical variations. The overall survival (OS) of the patients in the study was calculated. Only eligible patients were included in the analysis. Living patients were recorded until their last follow-up appointment. OS is defined from the date of HIV diagnosis to the date of death or the last follow-up if the date of death is absent. Survival curves were estimated to demonstrate OS using the Kaplan–Meier method. A log rank test was used to determine the factors that had an impact on survival rate. Logistic regression was used to create a predictive model using the collected parameters to estimate the probability of positive BME for infection. The statistically significant level was set at p-value < 0.05. The analysis was performed using SPSS software (SPSS version 11.5; SPSS, Chicago, IL, USA).

Results

Patient characteristics

Fifty-six HIV patients who had at least one BME after HIV diagnosis were identified. Thirteen of these had BME for hematological indication. Six had lymphoma and had lesions outside the BM definitely established by a pathologist. The latter had leukemia with high white blood cell counts in their blood. All these 13 patients were excluded. There were only 43 patients eligible in this study. Most were male (60.5%). The mean age was 36.7 years old (ranging from 21 to 66). Most (88.4%) had at least one prior episode of OI. Of these, TB was the most common infection (76.7%); therefore, the most common drugs prescribed were anti-TB drugs (67.4%). The other OIs included cytomegalovirus retinitis (CMV) and pneumocystis jirovecii pneumonia (PJP) (14% each). Only 15 patients (34.9%) received ARV. The frequency of hepatitis B and C coinfection was 14.3% and 26.5%, respectively (table 1). The median temperature in degrees Celsius for the 30 patients who had fever (69.8%) was 38.8 (ranging from 36 to 40.5). These patients were physically examined and approximately 70% were recorded as having LN (52.2%) and HS (52%). Only 4 patients (9.3%) had both findings concurrently (table 1). Average absolute CD4 count was 67.4 cell/mm3 (ranging from 0 to 604), but this parameter could be collected in only 36 cases. The mean total white blood cell (WBC) was 2,886 cell/mm^3 (ranging from 400 to 11,000). Twenty cases (46.5%) had an absolute neutrophil count (ANC), determined by calculation, of less than 1500 cell/mm^3. The percentage of neutrophil count less than 50% was 16.3%. The mean hematocrit (Hct) was 22.6% (ranging from 6% to 32.6%) which demonstrated that all included cases had anemia. The average mean corpuscular volume (MCV) was 82.3 fl (ranging from 69 to 123). Of these, 42% had a low MCV of less than 80 fl. The mean platelet count was 118,046 cell/mm^3 (ranging from 6,000 to 512,000). Thrombocytopenia, defined as platelet count less than 140,000, occurred in 67.4% of patients. The summary of these abnormalities including liver profile disorder was demonstrated by table 2. Only 6 cases had a high titer for CRAG; nevertheless, all demonstrated no pathological BME diagnosis for cryptococcosis. Half of the patients who had been diagnosed with this infection exhibited higher titer (1:1000). Hemoculture was performed in less than one-half of the cases. Only 3 patients were documented as TB-positive by hemoculture; all demonstrated no evidence of the agents in subsequent BME despite previous episodes of TB. One patient had a positive blood culture for fungus and was found to have histoplasmosis in his BM afterwards.

Results of bone marrow examination

The first BME was used for each patient to study. The median time from the date of HIV diagnosis to BME was 111 days. Twenty percent of the total undertook the procedure at the time of HIV diagnosis. Twenty-eight patients (65.1%) had hypocellular BM that was inappropriate for their age. Nearly half (47.4%) of the 38 cases for whom data was available for the ratio of myeloid and erythroid series (M:E ratio) in their BME had a ratio that was greater than 3:1. Plasmacytosis was also found in 91.4% of the patients. Of the one third

Table 1:

Characteristics of HIV patients with cytopenias

Demographics	Number of cases (%; n=43 unless otherwise stated)
Opportunistic infection OI[a] status	
Multiple OIs	13 (30.2)
Single OI	25 (58.1)
Absent	5 (11.6)
Type of OIs	
Tuberculosis	33 (76.7)
Pneumocystis jirovecii	6 (14)
Cytomegalovirus retinitis	6 (14)
Crytococcosis	3 (7)
Toxoplasmosis	3 (7)
Previous drugs	
Anti-TB	29 (67.4)
Sulfamethoxazole+Trimethoprim	20 (46.5)
Antiretroviral	15 (34.9)
Gancyclovir	5 (11.6)
Viral hepatitis status*	
Hepatitis B or C seropositive	11 (34.4)
Hepatitis B and C seropositive	1 (3.1)
Negative	20 (62.5)
Organomegaly	
Lymphadenopathy or Hepatosplenomegaly Both	17 (47.2)
Absent	4 (11.1)
	15 (41.7)

[a]OI: Opportunistic infection, *Missing Data in 9 patients.

Table 2:

Laboratorial results of HIV patients with cytopenias

Laboratorial results (Unit)	Result Mean(Range)
CD 4 (cell/mm3)	67.42 (0 - 604)
White blood cell (cell/mm3)	2,886.3 (400 -11,000)
Hematocrit (%)	22.6% (6 - 32.6)
Platelet count (cell/mm3)	118,046.5 (6,000 - 512,000).
Albumin (g/dL)	2.7 (1.2 - 4.2).
Alkaline phosphatase (IU/L)	271.5 (43 - 1173)

who was documented with a left shift in the myeloid series, 75% had plasmacytosis. These three conditions demonstrated the reactive process of BM in these patients. Of the 50% of cases that pathologist mentioned about dysplastic BM features, 80.9% tested positive. Megakaryocyte was mostly normal and was absent in only 5.7% of BME. Most BME also had iron deposit at normal to high levels; only 8% had no deposits. All of the cultures of BM blood for TB and fungus were negative. The BMEs were documented mostly as normal, secondary change or dysplastic feature or undetermined diagnosis in as much as 65%. For the 15 cases that had a BME diagnosis, the most frequent infection was TB (46.7%); all of these patients had a previous episode of TB. PJP and histoplasmosis accounted for 13.3% of samples each. Of those who were infected with PJP, none had been recorded as having this agent before. One patient who had a previous positive hemoculture for fungus was later found to have histoplasmosis in the BME but another did not. Mycobacterium avium complex (MAC) and Toxoplasmosis were each found in only one case (6.7%) that had never had any OIs or positive cultures. Pure red cell aplasia (PRCA) was found in 13.3% of samples (2 cases) which had extremely low levels of Hct (less than 10%) (table 3). These 15 cases that had a definite pathologic diagnosis would be used further in establishment of the model. Finally, there were 5 cases for which there were no clues except the finding obtained from the BME.

Survival

The median survival was 501 days. The final status of twenty-nine patients were recorded. Only 9 (20.9%) were alive at the end of this review. Organomegaly had been found to affect the survival rate (log rank test at p = 0.0053) for those who had both LN and HS versus those who had either or none (figure 1 and 2).

The estimation model

This model was designed to predict the probability of having BMI for HIV-infected patients who had concurrent cytopenias and especially those who exhibited no signs of OIs in their BM. The correlation between the parameters was first evaluated, with ALT was found to negatively correlate with Hct. Both parameters were excluded from the model. Subsequently, the total residue was entered and a logistic regression was performed. The ALP level was the most significant parameter to be decided firstly to enter in the model as forward style. The model was consecutively placed the latter significant parameters one by one. Finally, the most effective model estimation was obtained by including the ALP level, prior TB infection, and receipt of ARV therapy and presence of organomegaly[11]. The ALP level was the amount in terms of unit per liter. Having TB and receiving ARV were defined as 1. Zero was assigned if they had never occurred. For organomegaly, the placement value in the model was 2 for those who had both LN and HS, 1 for

Table 3:

Diagnosis by BM examination

Diagnosis	Number of cases (%; n=43)
Secondary change or Dysplastic/Unspecific	17/11 (65)
Tuberculosis	7 (16.3)
Pure red cell aplasia	2 (4.7)
Pneumocystic jirovecii	2 (4.7)
Histoplasmosis	2 (4.7)
Toxoplasmosis	1 (2.3)
Mycobacterium avium complex	1 (2.3)

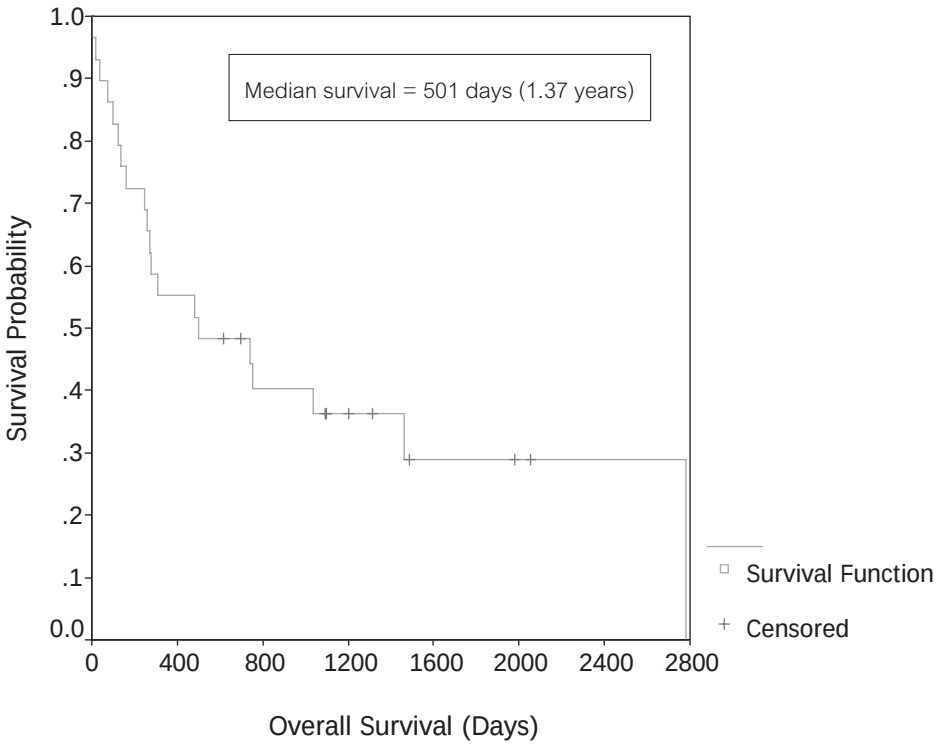

Figure 1: Kaplan-Meier curve demonstrating overall survival

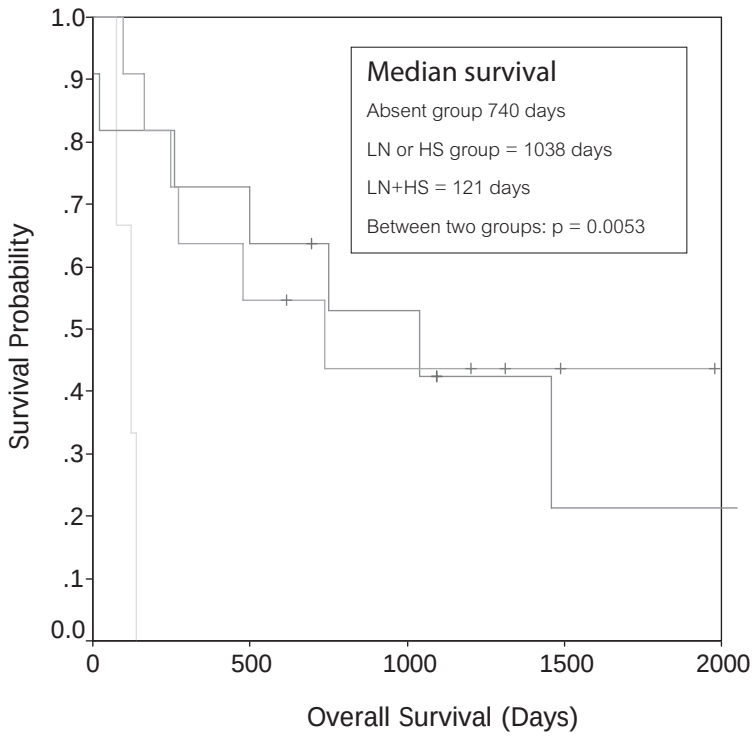

Figure 2: Kaplan-Meier curve demonstrating overall survival of patients with lymphadenopathy or hepatosplenomegaly (LN or HS), with presence of both (LN+HS) and absence

those who had either LN or HS, and 0 for those who had neither. The model estimation can be stated as follows:-

Odds of having BMI in HIV patients
= Exponential $^{[(0.009 \times \text{ALP level})^* + (3.555 \times \text{Organomegaly})^* + (3.358 \times \text{ARV})^{**} - (4.807 \times \text{TB})^* - 3.995^*]}$ .....(1)

* Statistically significant at < 0.05, ** p = 0.89

The probability of infection involved BM ** = Odds / (Odds+1).....(2)
** > 0.5 indicated that there was a BMI

The goodness of fit of the model was evaluated in many steps. The R^2 which was measured as 0.696 was fitted to this model to predict the real situation. The -2 Log likelihood was 19.334 which was the least level among any combinations for either parameter included in the model. The Hosmer and Lemeshow test was also insignificant. This model could predict the probability of BMI with an accuracy of 72.7% whereas the accuracy for exclusion of this condition was more than 91.3%. The overall accuracy of the prediction of the model was 85.3%.

Discussion

This study was conducted to determine patient characteristics, clinical course, and BME findings in HIV-infected patients who had cytopenias. Another objective was to pragmatically evaluate the value of BME for this condition in order to diminish the use of this tool as it appeared invasive and risky for patients, and also posed risks to those who performed the procedure and tested the specimens. The patients at risk were predominately adult males. Most had symptomatic HIV, were affected by OI and had a low CD4 levels as reported in previous studies[8,12]. TB was involved in these cases as were reported in many other previous studies. The patients were prescribed ARV before their BME in only 34.9% of cases. This may be due to an earlier type of treatment that tried to avoid immune reconstitution inflammatory syndrome (IRIS) by not giving ARV initially to patients with acute OI. Sungkanuparph et al. who rearranged Thai guide line for these patients mentioned this change according to international data update[13]. Most of our patients had been exposed to OIs adjacent to the time of HIV diagnosis and/or BME. A limitation of this study is that CD4 levels in patients first time diagnosed with HIV was not determined. Therefore, there was not enough data to determine if they might have a substantial CD4 level though not enough to require an ARV prescription at that time. Most patients had fever at the time of their BME; some were affected for a few weeks preceding the procedure. The information was incomplete because of the retrospective study method used to determine whether the fever was prolonged or not. Some of the cases had already provided evidence of OI outside the BM but BME was still performed for additional information. It seems that our subjects were performed BME earlier than those in the former studies which BME was indicated for fever of unknown origin (FUO)[8,12,14]. In these studies, most stated that the value of BME was insufficient to document any causes of cytopenias despite no other diagnostic tools for solving the problem. Coinfection with HBV and HCV were found in 14.3% and 26.5%, respectively. Coinfection with both was found in only one case. This is consistent with prior research by Arribas et al. in Europe[15]. Coinfection with hepatitis virus did not correlate with the prediction of cytopenias in this trial. This may be due to small number of coinfection cases This trend is the same for the concurrence of LN and HS in only 4 patients despite a large number of patient with each involvement than in the previous study[16]. Sawhney M. found almost 50% of cases had single LN involvement in his and 25% to have HS. These abnormal cases were reported as being suspected of having OIs and were found to participate significantly in the established model. There is unpublished data from southern Thailand that found HS raising yield of BME in such patients which is consistent with the finding in the current study.

Anemia was found in all patients that had low CD4 and/or received promoting drugs as previously mentioned [2,3,17]. Anemia can affect survival as found in a previous report[18]. By multivariate analysis, restoration of anemia by using ARV was associated with increment of survival. Survival in current study was also relatively short. Neutropenia and thrombocytopenia were found in approximately half of the cases. This result is higher than in the previous studies[3,19,20]. Nearly half of the patients had low MCV but their iron deposits in their BME were depleted in only 8%. MCV less than 80 fl was reported to be a risk factor that has the potential to cause anemia[18]. It may be caused by malnutrition and disorder of iron preservation upon chronic infection in HIV patients. Fortunately, the mean MCV was greater than 69 fl that was higher than that found in obvious iron deficiency and congenital anemia like thalassemia. The drawback was that there were no recorded laboratory results for other causes of anemia, such as erythropoietin, vitamin B, and folic acid. Higher ALT level and hyperbilirubinemia were found in 50% and 16.3% of cases, respectively. They may have been caused by adverse drug reactions, especially anti-TB and/or toxic liver hepatitis and cholestasis from any systemic infection involving liver. There was no documentation to discriminate these etiologies according to our retrospective study design. ARV was found to be another precipitating cause of abnormalities of liver enzymes[21]. ALP level in this trial was higher than in the former studies in Thailand. It was also stated as a predictor for a decision to proceed with a BME as in this study. The escalation was caused by ARV[21] and OI, especially as MAC infection described in many prior researches. Our study has found only 1 case of MAC. TB was stated in a recent report from our hospital[22]. Finally, the mean ALB level was low which demonstrated malnutrition status in these cases.

BME was mostly demonstrated as a hypocellular feature in contrast to other studies[18,19,23]. Most previous studies was derived from South Asia and demonstrated the finding as normal to hypercellularity, relatively. Reactive BM was shown to have the same characteristics of higher M:E ratio, left shift of myeloid series, and plasmacytosis as earlier studies[17,19]. Chronic infection and chronic inflammation may be the factors that promote these reactions. The alteration of stem cell maturation can result in blood cell dysplasia. Our study found prevalence of 81%, greater than the previous studies by Tripani et al. that was only 16.67%[19].

CRAG and TB-hemoculture positives do not predict BME findings for the agents. All of them were only confirmed history of each infection; therefore, both seem to be of little value to perform for those who had prior episodes of infection. One of the two patients who had a positive hemoculture for fungus was later found to have histoplasmosis on his BME. A BME for this patient would be of limited value because there is no difference in treatment between having only septicemia and having it concurrently with BM. All of the BM blood cultures were negative. The yield was also reported to be low in earlier research[24,25,26]. The predictive value upon hemoculture of either BM or peripheral blood should be reconsidered. There were few cases that this test was performed and had data available to evaluate. Only one-third of included patients had documented BMI. TB was the majority of BMI as some previous research[7,8,17]. All of the patients had previous episodes of TB infection in spite of their negative TB culture at the time of BME upon blood stream and BM blood. Histoplasmosis, PJP, toxoplasmosis and MAC had accounted for the remaining. Conclusively, only 12% had a yield from BME, mostly because of the absence of any hints of OIs and previous documentation of corresponding agents in this study. This trend is consistent with some earlier reports[8] but has a lower yield than some others[7,14]. The latter studies proposed the yield is above 20%. As PRCA was demonstrated through BME in 2 cases, it is necessary to consider it in patient who is extremely anemic.

Median survival was about 16.7 months. After BME, the patients would die within 2.8 months Organomegaly was the only factor to have an impact on survival rates. For those who had both LN and HS, it may be assumed that some of the OIs in their body were more extensive. Only LN was found to be a risk factor that correlated with

survival in one study[27]. TB was found to be associated with this disorder.

As previously stated, there were only 35% of OI-infected cases that had the diagnosis proved by BME and only 33% of these had no evidence or history suggesting OIs outside BM. This group is the target group which requires BME to determine their infection. Predictive model estimation may be warranted in order to avoid procedures with little diagnostic value. To control some variations in the data that may have an abnormal distribution and promote the model serving categorical medical decision, logistics regression was used to create the model. All of the terms are statistically significant except for ARV which has a trend of $p = 0.89$[11]. A rise in ALP level and having organomegaly contribute to the chances of having BMI. For every increment of ALP level above the normal by 1 unit per liters, the chances of BMI increase by about 3.52 times. Having only LN escalates the odds 35 times and having both LN and HS raise it by 1,224 times. Receiving ARV enhances the odds of BMI by 29 times. ARV might reduce the viral load, escalate the CD4 level, and restore the cytopenic status. A possible explanation is that having cytopenias despite ARV may relate to drug resistance and consequently, increased risk of infection. Occult BMI is another factor that may precipitate the continued presence of cytopenias in spite of treatment by ARV. A history of having TB is counted as the last factor but is inversely correlated with BMI. This means that patients who have had TB have lower probability of BMI. In contrast, this study found that all six who had a BM diagnosis of TB were affected by it in the past, which requires further investigation. The possible explanation is that the overall number of patients with a prior episode of TB was greater than 33 cases whereas the rest had no documentation of any following BMI. This occurrence may have an impact on the model. More research is necessary to confirm this phenomenon and to duplicate the results for comparison purposes. In this model, having a history of TB reduces the risk of having BMI from 1 to 0.008. It was decided to keep TB in the model because it could help the ARV term to have a statistically significant trend and to raise the R^2 of the model by 10% which was the best value ever.

It is hoped that the predictive model estimation can help physicians make better decisions regarding BME. The study has several limitations such as small number of patients, retrospective study design, and lack of some data. Studies with more sample size are required to evaluate this model.

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Reference

1. Bain BJ. The Hematological features of HIV infection. Br J Haematol 1997; 99: 1-8.
2. Sloand E. Hematologic complications of HIV. AIDS Reviews 2005; 7: 187-96.
3. Hira SK, Kamanga J, Bhat GH. Perinatal transmission of HIV-1 in Zambia. Br Med J 1989; 299: 1250-2.
4. Volberding PA, Baker KR, Levine AM. Human immunodeficiency virus hematology. Hematology Am Soc Hematol Educ Program 2003: 1; 294-313.
5. Cosby CD. Hematologic disorders associated with human immunodeficiency virus and AIDS. J Infus Nurs 2007; 30: 22-32.
6. Fernandez-Aviles F, Ribera JM, Romeu J, Batlle M, Navarro JT, Manterola JM, et al. The usefulness of the bone marrow examination in the etiological diagnosis of prolonged fever in patients with HIV infection. Med Clin (Barc) 1999; 112: 641–5.
7. Llewelyn Mj, Noursedeghi M, Dogan A, Edwards SG, Miller RF.. Diagnostic utility of bone marrow sampling in HIV-infected patients since the advent of highly active antiretroviral therapy. Int J STD AIDS 2005; 16: 686-9.
8. Santos ES, Raez LE, Eckardt P, DeCesare T, Whitcomb CC, Byrne GE Jr. The Utility of a Bone Marrow Biopsy in Diagnosing the Source of Fever of Unknown Origin in Patients with AIDS. J Acquir Immune Defic Syndr 2004; 37(5): 1599-603.
9. Keiser P, Rademacher S, Smith JW. Utility of bone marrow culture and biopsy in the diagnosis of dissiminated infections in AIDS. Am J Hematol 1997; 56: 1-4.

10. Kilby JM, Marques MB, Jave DL, Tabereaux PB, Reddy VB, Waites KB. The yield of bone marrow biopsy and culture compared with blood culture in the evaluation of HIV-infected patients for mycobacterial and fungal infections. Am J Med 1998; 104: 123-8.
11. Hair JF, Black WC, Babin BJ, Anderson RE. Multivariate data analysis 7th ed. New Jersey: Pearson Education Inc.; 2010: 317-42.
12. Tanaka PY, Hadad DJ, Barletti SC, de Souza SA, Calore EE. Bone marrow biopsy in the diagnoses of infectious and non-infectious causes in patients with advanced HIV infection. J Infect 2007; 54(4): 362-6.
13. Sungkanuparph S, Anekthananon T, Hiransuthikul N, Bowonwatanuwong C, Supparatpinyo K, Mootsikapun P, et al. Guidelines for Antiretroviral Therapy in HIV-1 Infected Adults and Adolescents: The Recommendations of the Thai AIDS Society (TAS) 2008. J Med Assoc Thai 2008; 91(12): 1925-36.
14. Pande A, Bhattacharyya M, Pain S, Ghosh A, Samanta A. Diagnostic yield of bone marrow examination in HIV associated FUO in ART naïve patients. J Infect Public Health. 2010; 3(3): 124-9.
15. Arribas JR, Gonzalez-Garcia JJ, Lorenzo A, Montero D, Ladron de Guevara C, Montes M, et al. Single (B or C), dual (BC or BD) and triple (BCD) viral hepatitis in HIV-infected patients in Madrid, Spain. AIDS 2005; 19; 1361-5.
16. Sawhney M. Lymphoreticular Involvement in Human Immunodeficiency Virus Infection. Med J Armed Forces India 2008; 64: 4-6.
17. Khandekar MM, Deshmukh SD, Holla VV, Rane SR, Kakrani AL, Sangale SA, el al. Profile of bone marrow examination in HIV/AIDS patients to detect opportunistic infections, especially tuberculosis. Indian J Pathol Microbiol. 2005; 48 (1): 7-12.
18. Berhane K, Karim R, Cohen MH, Masri-Lavine L, Young M, Anastos K, et al. Impact of highly active antiretroviral therapy on anemia and relationship between anemia and survival in a large cohort of HIV-infected woman: Women's Interagency HIV study. J Acquir Immune Defic Syndr 2004; 37: 1245-52.
19. Tripathi AK, Kalra P, Misra R, Kumar A, Gupta N, et al. Study of bone marrow abnormalities in patients with HIV disease. J Assoc Physicians India 2005; 53: 105-10.
20. Dikshit B, Wanchu A, Sachdeva RK, Sharma A, Das R. Profile of hematological abnormalities of Indian HIV infected individuals. BMC Blood Disord. 2009 Aug 13; 9: 2326-9
21. Analike RA, Nnamah NK, Dioka CE, Medludu SC , Osuji CU, Asomugha AL. Evaluation of liver function tests of HIV-positive patients on antiretroviral therapy in Nnewi, Nigeria J Biomed Inv 2006; 4(2): 42-8.
22. Shimisu K. Fever with elevated alkaline phosphatase in HIV/AIDS patients at Chonburi regional hospital, Thailand [Dissertation]. Bangkok: Mahidol University; 2001.
23. Pande A, Bhattacharyya M, Pain S, Samanta A. Study of bone marrow changes in antiretroviral naive human immunodeficiency virus-infected anemic patients. Indian J Pathol Microbiol 2011; 54: 542-6.
24. Duong S, Dezube BJ, Desai G, Eichelberger K, Qian Q, Kirby JE. Limited Utility of Bone Marrow Culture: A Ten-Year Retrospective Analysis. Lab Med 2009; 40(1): 37-8.
25. Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med. 2003; 163: 545–51.
26. Pacios E, Alcala L, Ruiz-Serrano MJ, de Viedma DG, Rodrıguez-Creixems M, Marın-Arriaza M, et al. Evaluation of bone marrow and blood cultures for the recovery of mycobacteria in the diagnosis of disseminated mycobacterial infections. Clin Microbiol Infect. 2004; 10: 734–7.
27. Richter C, Koelemay MJ, Swai AB, Perenboom R, Mwakyusa. DH, Oosting J. Predictive markers of survival in HIV-seropositive and HIV-seronegative Tanzanian patients with extrapulmonary tuberculosis. Tuber Lung Dis. 1995 Dec; 76(6): 510-7.