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การศึกษาลักษณะไขกระดูกและผลลัพธ์ทางคลินิกในผู้ป่วยมะเร็งเม็ดเลือดขาวเรื้อรัง multiple myeloma

Bone marrow findings and clinical outcomes of the multiple myeloma: A retrospective study

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บทคัดย่อ

วัตถุประสงค์ : งานวิจัยนี้แสดงอัตรารอดชีพของผู้ป่วยมะเร็งไขกระดูกมัยอิโลมา รวมถึงความสัมพันธ์ของปัจจัยต่างๆ ทางการตรวจพยาธิวิทยาและมัธยฐานระยะเวลาความอยู่รอด

รูปแบบและวิธีวิจัย : การศึกษาย้อนหลังศึกษาในไขกระดูกของคนไข้ที่ได้รับการวินิจฉัยทางพยาธิวิทยาเป็นมะเร็งไขกระดูกมัยอิโลมาครั้งแรกทั้งหมด ตั้งแต่ 1 มกราคม 2551 จนถึง 31 ธันวาคม 2562 ในโรงพยาบาลศรีนครินทร์ มหาวิทยาลัยขอนแก่น

ผลการศึกษา : ผู้ป่วยจำนวน 253 คนมีอัตราการรอดชีพคิดเป็นมัธยฐานระยะเวลาความอยู่รอดที่ 2.12 ปี (ค่าความเชื่อมั่น 95%: 1.83 – 2.64 ปี) ผู้ป่วยจำนวน 44 คน (17.4%) ซึ่งมีลักษณะของเซลล์มะเร็งพลาสมาเป็นกลุ่มยังไม่เจริญเต็มที่ มีการดำเนินโรคแย่กว่ากลุ่มที่มีลักษณะของเซลล์มะเร็งเจริญเต็มที่ โดยมีมัธยฐานระยะเวลาความอยู่รอดที่ 1.83 ปี (ค่าความเชื่อมั่น 95%: 0.70 – 2.17) และ 2.44 ปี (ค่าความเชื่อมั่น 95%: 1.83 – 3.01) ตามลำดับอย่างมีนัยยะสำคัญทางสถิติ (p-value 0.0297) (อัตราส่วนความเสี่ยงอันตราย 1.5, ค่าความเชื่อมั่น 95%: 1.04 – 2.18, p-value 0.031)

สรุปผลการศึกษา : ลักษณะของเซลล์มะเร็งพลาสมาที่เป็นกลุ่มยังไม่เจริญเต็มที่ ส่งผลต่อการพยากรณ์โรคที่แย่กว่ากลุ่มที่เจริญเต็มที่ แม้ว่าจะมีโอกาสพบในคนไข้น้อยกว่ามาก

คำสำคัญ : มะเร็งจากพลาสมาเซลล์, ลักษณะของพลาสมาเซลล์, มะเร็งไขกระดูกมัยอิโลมา, การศึกษาลักษณะไขกระดูก, โอกาสรอดชีพ

ABSTRACT

Objectives : Our study primarily describes the survival of multiple myeloma (MM) patients and focuses about the correlation between these findings using various pathological parameters and clinical outcomes as median survival time.

Methods : Our retrospective study includes all bone marrow biopsy samples with pathologically proven first-diagnosis plasma cell neoplasm from 1st January 2008 to 31st December 2019 at Srinagarind Hospital.

Results : 253 first-diagnosis plasma cell neoplasm cases underwent survival analysis showing the median survival time was 2.12 years (95%CI: 1.83 - 2.64 years). Forty-four cases (17.4%) showed intermediate and immature neoplastic morphologies affecting the adverse outcome compared with the mature group exhibiting the median time survival was 1.83 years (95% CI: 0.70 - 2.17) and 2.44 years (95% CI: 1.83 - 3.01), respectively (p-value 0.03) (HR 1.5, 95%CI: 1.04 - 2.18, p-value 0.03).

Conclusions : Even though much less frequently, the morphology of neoplastic plasma cells, particularly the immature group, still has an impact on the poorer prognosis.

Keywords : Plasma cell neoplasm, plasma cell morphology, multiple myeloma, bone marrow finding, overall survival

Introduction

Multiple myeloma (MM) is considered the third most common hematologic malignancy beside non-Hodgkin lymphoma and leukemia[1,2], which account for 1,411 new cases in Thailand per year in 2020[2]. Nowadays, the treatments of MM patients include autologous stem cell transplantation, immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) can significantly prolong overall survival and disease-free survival of the patients[1]. However, MM remains an incurable disease, and all myeloma patients will eventually relapse and refractory to available treatment.

Many prognostic factors of myeloma patients were elucidated which include bone marrow plasma cell morphology[3–10], tumor burden[9,11], degrees of fibrosis[12–14]. The cytogenetics of the tumor, demographic data, and therapeutic response were additional important prognostic indicators[11]. Besides neoplastic clones, other bone marrow components, called as the microenvironment including microvessel density[9,13,15] and degree of fibrosis[12], come to the interesting factors that affect the survival of the patient including tumor differentiation, migration, proliferation, and drug resistance[16] . The above-mentioned factors lead the median overall survival (OS) of approximately 5 to 7 years for myeloma patients.

Neoplastic cellular morphology produces adverse effects on overall survival, degree of fibrosis, and level of cyclin D1 expression[12,17]. Furthermore, the patients with the plasmablastic group showed advanced clinical manifestations including severe anemia, renal insufficiency, high serum beta2 globulin, and hypoalbuminemia[18]. However, the addition of morphological studies in the Asian population, clinical outcome correlation, and other valuable data for further research are still required to elucidate. In our study, we determined the correlation between the biopsy findings of the first-diagnosed multiple myeloma patients and the clinical outcomes, sub-grouped by each parameter, using survival analysis.

Materials and methods

Study population

The study retrospectively comprised all bone marrow biopsy samples with pathologically proven firstly diagnoses the plasma cell neoplasm from 1st January 2008 to 31st December 2019 at Srinagarind Hospital, regardless of age group, gender, or birthplace. Reviews of all cases from the past were conducted. Recut sections from the formalin-fixed paraffin-embedded (FFPE) tissue blocks were performed to reveal any pathological features that concealed or morphology, which was unacceptable. Cases without a tissue block, historical data proven not the firstly diagnoses cases, or inappropriate morphology in a recut section including poorly fixative tissue, artifacts, and no remaining neoplastic cell, were excluded from this study.

Morphological findings evaluation and operational definition

One anatomical resident and one board-certificated hematopathologist evaluated plasma cells tumor morphology, inclusion bodies, and tumor percentage, independently. Any discordant situations, such as different grouping of the neoplasm, were discussed and assigned to the proper group. The plasma cell morphologies were divided into three groups including mature-, intermediate-, and immature morphologies according to the presence of plasmablastic or immunoblastic morphologies[6]. The tumor infiltration percentage was subclassified into three groups: Less than 20%, 20% to 50%, and more than 50% of the cellular area, respectively[6,19] (table 1).

Operational definition	Definition
Neoplastic morphologies	
Well-differentiated (Mature)	Plasmacytic cells are well-differentiated with an eccentric nucleus, small or absent nucleoli, intact perinuclear halo and basophilic cytoplasm.
Intermediate	Pleomorphic in nuclear size and cellular neoplastic cells are noted, the nuclear position is less eccentric. Large nucleolus can be presented. Perinuclear halo can be absent.
Poorly-differentiated (Immature)	Uniformly plasmablastic cells presented with prominent large centrally located nuclei. Perinuclear halo is absent.
Tumor percentage	
Mild	Neoplastic plasma cells are less than 20% of cellular area
Moderate	Neoplastic plasma cells are between 20%-50% of cellular area
Marked	Neoplastic plasma cells are more than 50% of cellular area

Table 1: Pathological parameters for pathological evaluation and each operational definition

Statistical analysis

Patients' dates of diagnosis were recorded and followed up until they either passed away or lost contact until 31st December 2021. The collected data were analyzed using the statistical software STATA (version 10.1, KKU license). Categorical data was demonstrated in the form of the percentage, while continuous data was recorded as a range. Survival analysis between each subgroup was analyzed by the Kaplan-Meier estimator and COX proportional hazards regression. Median survival time and hazard ratio were analyzed within a part of the survival analysis. A significant result was considered with the p-value less than 0.05.

Ethical consideration

This study protocol and case record form were approved and accepted by the Ethical committees for Research in Human Subjected at Srinagarind hospital.

Results

Three hundred and six cases of pathologically proven plasma cell neoplasm between 1st January 2008 and 31st December 2019 at Srinagarind Hospital were enrolled. Fifty-three cases were excluded as follows: inaccessibility of formalin-fixed paraffin-embedded (FFPE) tissue block (35 cases), unsatisfactory specimen preservation on recut H&E section (15 cases), and incomplete material and patient's data (3 cases). The 253 remaining cases were subsequently accessed the pathological and morphological findings. The 191 cases passed away (75.49%), while the remaining 62 cases (24.50%) were alive on 31st December 2021. The median follow-up time of the patients were 23 months. Basic demographic data of the patients and bone marrow findings of the neoplasm were demonstrated in the table below (table 2). The examples of the neoplastic cell morphologies were demonstrated in the figure (figures 1 and 2).

Demographic data	n	Percentage
Gender		
Female	111	43.9
Male	142	56.1
Age (year)		
Median (range)	60 (30 - 86)	
Plasma cell morphology		
Mature	209	82.6
Intermediate and Immature	44	17.4
Tumor percentage		
Up to 50%	27	10.7
More than 50%	226	89.3
Inclusion body		
Absence	167	66
Presence	86	34

Table 2: Demographic data and bone marrow pathological findings

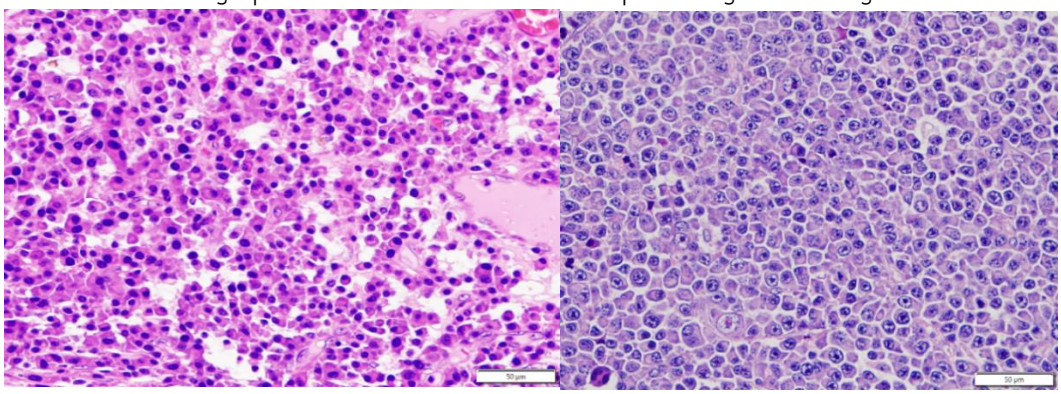

Figure 1 (Left): Well-differentiated plasma cell neoplasms showed monotonous proliferation of the mature-looking plasma cell (H&E stain: 40X)

Figure 2 (Right): Poorly differentiated plasma cell neoplasms showed monotonous proliferation of the plasmablastic and immunoblastic morphologies (H&E stain: 40X, plasma cell lineage was confirmed by diffuse strongly expressed CD138 on the cell membrane (not show))

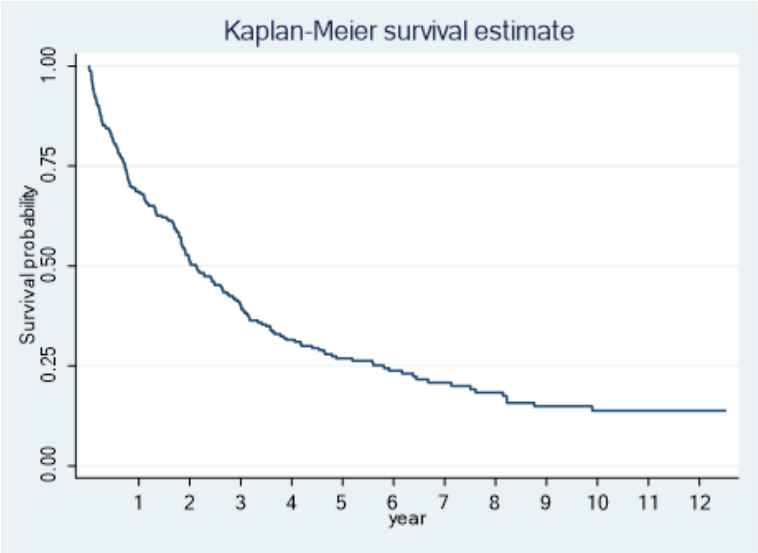

Figure 3: Kaplan-Meier survival estimate the overall survival (OS)

Figure 3 shows a Kaplan-Meier graph depicting overall survival, with the patient median survival time estimated approximately 2.12 years (95%CI: 1.83 - 2.64 years).

When aging increased, the COX proportional hazard evaluation by age showed a much worse survival outcome, significantly (HR 1.03, p-value less than 0.001, 95%CI: 1.01 – 1.04).

According to subgroup analysis, patients with intermediate and immature plasma cell groups had shorter median OS (1.83 years, 95% CI: 0.70 - 2.17) than those with mature plasma cell groups (2.44 years, 95% CI: 1.83 - 3.01) (p-value 0.0297) (figure 4). The hazardous ratio using COX regression was 1.5 (p-value 0.031, 95%CI: 1.04 - 2.18).

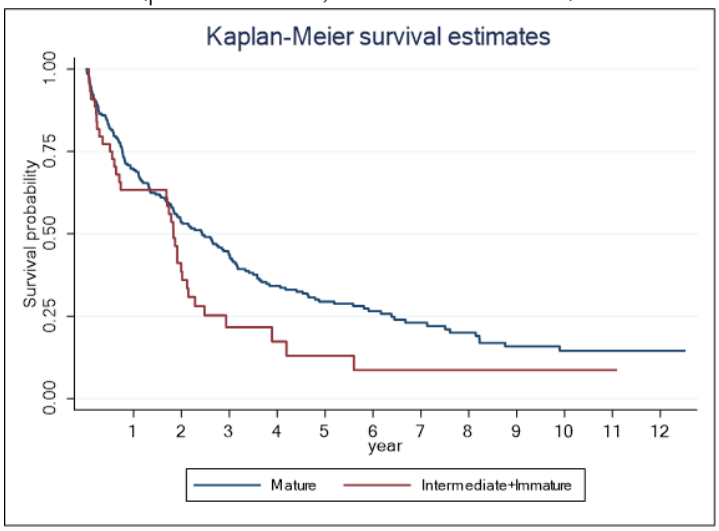

Figure 4: Kaplan-Meier survival estimator sub-grouped by neoplastic morphologies

Other pathological parameters including the percentage of the neoplastic cell infiltration, presence of inclusion body, and gender did not show significantly affected median OS of the patient (p-value 0.170, 0.169, and 0.496, respectively)

Discussion

Our study also supported the correlation between the plasmablastic morphology of the neoplasm and the poor prognosis of the patients. Increased in patient's age also affected the clinical outcome, which was correlated with the previous studies[3–10]

The median age of patients receiving their first diagnosis at Srinagarind Hospital was 60 years and the gender proportion of patients showed slightly male predominant, which both results were consistent with the previous studies[7,9,20,21]. Even though we included all relevant pathology data in this research, there were a few patients diagnosed at other institutions and some missing data, resulting in fewer patients being enrolled in the study than the actual number of patients treated.

The accessibility of FFPE tissue blocks became the key necessary material in our study and the fundamental demographic information was gathered by the limited condition using pathological requests to retrospectively recruit all biopsy-proven populational cases. Other important patient data that affected median OS such as the ECOG score, myeloma defining event, ISS score, treatment line, response to treatment, and cytogenetic risk, were not analyzed and stratified due to the limitation to access the medical records and unavailable genetic evaluation. We encouraged further studies to combine more pathological and clinical correlation as well as cytogenetic evaluation together.

The majority of the plasma cells morphology was mature-looking, eccentrically located nuclei, visible perinuclear halo, and inconspicuous nucleolus, which were identical to the previous studies[3,5–7,10]. The minority population was an immature group, which had a tendency to correspond with a high tumor infiltration percentage in our observation but without statistical significance (p-value 0.187). We also observed that the neoplastic growth pattern of the immature group was majority diffuse and created space-occupying lesions disrupting adjacent structures without interstitial distribution in contrast to some of the mature type behaved. Inclusion bodies were less observed in the immature group. The additional bone marrow findings including degrees of fibrosis or angiogenesis and amyloid deposition were not performed in our study due to the limitation in the additional tissue section.

In contrast to the earlier study, the median patient survival time in this study was 2.12 years, compared to approximately 5-7 years in other research[9,11]. According to 12 years retrospective review, most MM patients had the limitation to access novel therapeutic agents and few of them were unavailable to assess the chemotherapy treatment line. We also identified the volume of neoplastic infiltration using percentage by cellular area, which was

more practical in our institute, and 89.3% of the patients suffered from neoplastic cell infiltration greater than 50% of the cellular area. These results might be presented as adverse outcomes causing much shorter median time survival in our population.

Our study also provided evidence that the higher age at first diagnosis and immature neoplastic morphology affected the shorter median OS of MM patients, which supported the previous studies[3–7,9,10]. Immature neoplastic morphology correlated with cyclin D1 overexpression, extensive tumor infiltration, high proliferative index, and complex karyotype including del(13q)[6,8].

An inadequate number of patients in this study was a limitation for the powerful demonstrating statistically significant. However, the percentage of neoplastic plasma cells in the bone marrow and plasma cell inclusion body seemed to affect the prognosis. We also recommended expanding the population and well-stratifying other factors affecting median OS for the further studies.

Conclusion

Older age group and immature neoplastic plasma cell morphology correlate with the shorter median OS in out institution.

Clinical practical point

Our study emphasizes pathologist concerning about bone marrow findings of myeloma patients and anticipates the future additional integration of molecular and cytogenetic analyses, which leading to the best course of treatment for the patient.

Disclosure

The authors have no conflict of interest to disclose.

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