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Multiple Myeloma: Modification and Adaptation of Plasma Cell Morphology Algorithm for the Prognosis of Congolese Patient

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Abstract

Objectives: To determine the multiple myeloma (MM) prognostic formulas applicable in Congolese with many aberrant and/or immature plasma cells according to GOASGUEN's plasma cell morphology algorithm (PMA). **Methods:** The prospective, observational and descriptive study was carried out at the Ngaliema Clinic in Kinshasa from July 2016 to December 2019. The variables studied were the plasma cell types and the prognosis groups according to GOASGUEN and ZANDECKI. The nucleolus, the chromatin and the N/C ratio of 2 for each plasma cell encountered in multiple myeloma are examined in order by asking three successive questions as follows: 1) Is the nucleolus present? If yes, we denote 1; if not, note 0; 2) Is the chromatin thin? If yes, we score 1; if not we score 0; 3) The N/C ratio is greater than 6, if so, 1 is noted; if not, we note 0. We obtain a number with 3 successive digits preceded by the letter P for each plasma cell. **Results:** The overall rate of immature plasma cells and aberrant plasma cells in MM among Congolese was high at 26.6%. Their integration in the prognostic formulas showed for group A" = 22 patients, group B" = 5 patients and group C" = 32 patients. Examination of plasma cell types in the deceased showed that 14/17 had a P001 plasma cell count ≥ 15%. **Conclusion:** The high rate of aberrant and/or immature plasma cells, the P001 plasma cell type at a rate ≥ 15%, found mostly in group C" with poor prognosis, are responsible for the aggres-

sive nature of MM in Congolese Blacks.

Keywords

Plasma Cell Morphology Algorithm, Plasma Cell Types, Aberrant Plasma Cells, Immature Plasma Cells, Multiple Myeloma

1. Introduction

The aim of this study was to complete our previous study, published under the title "plasma cell morphology in multiple myeloma" [1]. We used a new cohort of 59 patients, with multiple myeloma over a three-and-a-half-year period.

The following operations were performed; the myelogram and the count of plasma cells according to the three criteria of PMA, the integration of the immature plasma cell P101 and the aberrant plasma cell P001 in the prognosis formulas, the evaluation of the impact of P001 ≥ 15% on early death, the determination of survival patients according to the different types of plasma cells encountered.

2. Patients and Methods

2.1. Patients, Type and Setting of the Study

This study was performed on bone marrow smears from 59 patients Black, and Congo citizen with multiple myeloma: 31 men and 28 women whose ages varied between 43 - 82 years for men and between 19 - 69 years for women. These patients were referred from different medical Centers in Kinshasa City to the Laboratory of the Ngaliema Clinic in Kinshasa from July 2016 to December 2019.

2.2. Methods

The patients selected for the study had multiple myeloma based on bone marrow smear examination. The study was prospective, observational and descriptive. The enumeration of the plasma cell types of the patients was carried out on the basis of PMA with three following criteria in the presence of the nucleolus, the presence of fine chromatin and the N/C ratio of the plasma cells found [2]. Thus, the most frequently encountered plasma cells were all integrated into Goasguen's prognosis formulas to determine the evolution of patients in the different prognosis groups. The observation of plasma cells found in deceased patients was of great help in discovering the impact of plasma cell P001 ≥ 15% on early death.

For operational reasons, we will use the following terms:

Prognosis: to define the theoretical evolution of patients with Goasguen's formulas;

Become: for all the patients of this study whose situation was evaluated, whether they are alive, lost to follow-up or deceased;

Survival: to define the course of living and deceased patients in this study.

Patient survival: is duration between the date of diagnosis and the date of death or the date of the last follow-up of the living patient. This duration is eva-

luated in number of months. The dates of diagnosis are recorded in a register. For the dates of death, we obtained them through telephone surveys through families. This regular and annual assessment ended in January 2021.

3. Results

3.1. Types of Plasma Cells Found

We used the PMA to enumerate the different types of plasma cells of patients before classifying them in the prognosis groups. We found that the four most frequent types were always the same as in our previous work [1]; these were P000, P001, P100 and P101 which together represented 96.7% of the plasma cells found. The other plasma cells P011, P111, P110 and P010 represent only 3.3%. These results are shown in **Figure 1**.

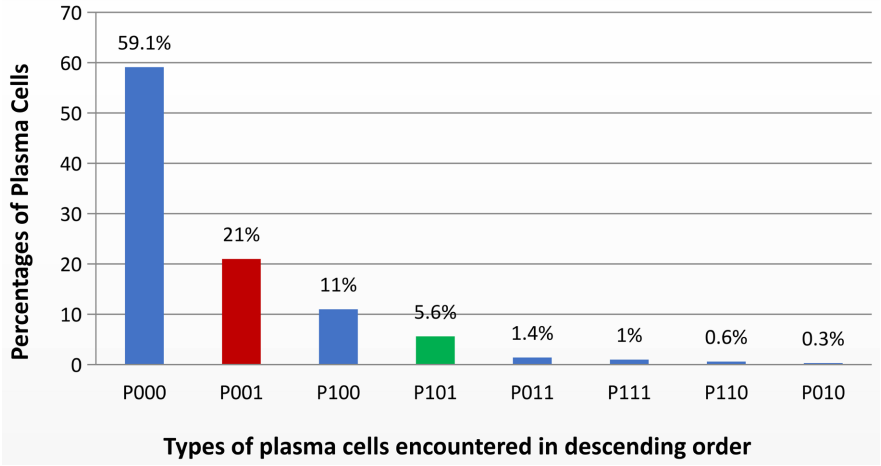

Figure 1. The most frequent types of plasma cells in our environment. Legend: P000 = mature plasma cell; P001 = aberrant plasma cells, P100 = proplasmocyte I; P101 = immature plasma cells and P111 = plasmablast.

3.2. Original Multiple Myeloma Prognosis Formulas

By grouping the patients according to Goasguen's original multiple myeloma prognosis formulas, we ended up with 32 patients in group A of Good responders, 20 in group B Intermediate and 7 in group C of Poor responders. These original formulas include 1 or 4 types of plasma cells and are as follows:

Group A: P000 ≥ 66% with P111 < 2%;

Group B: P000 < 66% and P100 ≥ P110 + P111 with P111 < 2%;

Group C: P000 < 66% and P100 < P110 + P111 with P111 ≥ 2%.

With P111 ≥ 2% as an independent element of poor prognosis.

These original formulas do not take into account P101 or P001 which together represent 26.6% of the plasma cells of our patients.

3.3. Prognosis of Multiple Myeloma after Integration of P101 in the Group Formulas

Taking into account the number of immature plasma cells P101, in the formulas

of the prognosis groups was essential. Thus, the new formulas were written as follows:

Group A': P000 ≥ 66% with P111 < 2%;

Group B': P000 < 66% and P100 ≥ P110 + P111 + P101 with P111 < 2%;

Group C': P000 < 66% and P100 < P110 + P111 + P101 with P111 ≥ 2%.

By applying these new formulas of prognosis prognostic group [1], we saw that the first group A, group of Good responders, had remained with its 32 patients (it becomes Group A'), the second B decreased from 20 to 13 patients (it became Group B') and finally; the third group C, called group of Poor responders, had increased from 7 to 14 patients (it became Group C').

3.4. Impact and Significance of P001 ≥ 15% on the Prognosis Established with P101

Based on the survival observed patients the formulas with P101, counting the number of deaths before 18 months, we observed that there were 8 deaths in the first group A', 3 deaths in the second group B' and 6 deaths in the third group C'. This gave a total of 17 deaths within 18 months.

The examination of the plasma cell types in the deceased individuals of these three groups of prognosis of new formulas showed that 14 people out of the 17 had in common a level of plasma cells P001 ≥ 15% of the plasma cells encountered in each of them. These 14 people accounted for 87.5% of deaths in 18 months and 23.7% of the total of all patients. These were 5 deaths of group A', 3 deaths of group B' and 6 deaths group C'.

This showed that people with a short true survival, regardless of the group, had in common a rate of plasma cells P001 ≥ 15%. Thus, the plasma cell P001 at the level ≥ 15% is thus considered by us as a plasma cell linked to early death. Thus the rate of P001 ≥ 15%, regardless of the group, was an independent factor of poor prognosis as is P111 ≥ 2%.

3.5. Integration of P001 in the Formulas of the Prognosis Groups

Taking into account the number of P001 which represented 21% of plasma cells in the distribution, and the influence of plasma cell P001 ≥ 15% on short-term death, we included all of P001 in the prognosis formulas as we did for P101 and transferred P001 ≥ 15% to the group of poor responders with short median survival. Thus, the different formulas of the prognosis groups have become:

Group A" = *P000* ≥ 66%; *with* P001 < 15% and P111 < 2%;

Group B" = *P000* < 66% *and P100* ≥ *P110* + *P111* + *P101* + *P001* + *X*; *with* P001 < 15% and P111 < 2%.

Group C" = *P000* < 66% *and P100* < *P110* + *P111* + *P101* + *P001* + *X*; with *P001* ≥ 15% and/or P111 ≥ 2% as independent elements of poor prognosis.

Under certain conditions X which represents P010 and P011 could also be integrated in the formulas of prognosis groups if its level is increased.

After this distribution, we found that out of a total of 59 patients, 22 remained

in the first group A", 5 in the second group B" and 32 in the third group C" as can be seen in Figure 2. In addition, the observation showed that the patients of this third group C" had the following characteristics: 27 patients with P001 ≥ 15%, 3 patients with P111 ≥ 2% + P001 ≥ 15%, 1 patient with P111 ≥ 2% and 1 patient with P101 + P100. This showed that this set consisted of all the patients with immature plasma cells and/or aberrant plasma cells in large numbers.

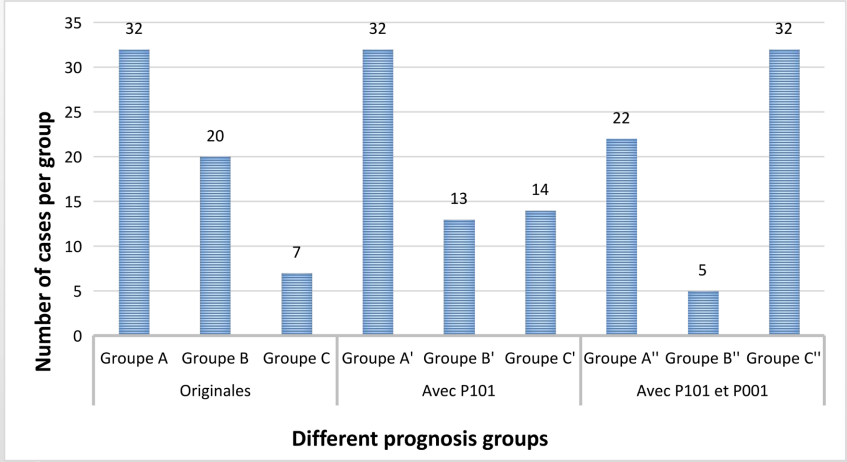

Figure 2. Prognosis groups with original formulas and prognosis groups after successive integrations of P101 and P001.

4. Patients of Different Groups after Integrations

4.1. Becoming Group A" Patients

Group A" was the first group, it contained 22 (37.3%) patients. This group was that of Good Responders. In this group, the fate of the patients was distributed as follows; there were 4 deaths (6.8%) at 12 months, 14 months, 20 months and 38 months. The lost to follow-up represented 10 patients (16.9%) and finally 8 patients (13.6%) alive at the time of writing this work were grouped as follows:

3 living patients were alive for 19 months for two and 23 months for one.

2 living patients were alive for 27 months and 35 months.

3 living patients were alive for 38 months for two, then 45 and 49 months.

4.2. Becoming Group B" Patients

Group B" is the intermediate or second group. It included 5 patients among whom, there were 2 surviving (3.4%) with 23 months of survival, 1 death (1.7%) at 10 months and 2 lost (3.4%) to follow-up.

4.3. Become Group C" Patients

In this group C" or group of poor responders of 32 (54.2%) of the 59 patients who participated in the study, 14 deaths (23.7%) were recorded within 18 months, 8 patients (13.6%) were lost to follow-up, 10 others (16.9%) were alive, including 6 patients (11.2%) of them, were still being treated here in the country, among them 5 whose survival time was about 14 months and 1 whose lifespan

was over 26 months. The remaining 4 patients (6.8%) had followed an alternative treatment abroad, especially in Morocco and India, their survival is respectively 36 months, 24 months, 30 months and 46 months. All of these results are shown in Table 1.

4.4. Alive and Deceased from Different Groups

The living and the deceased are shown in Table 2, divided into their different prognosis groups established after the integration of P101 and P001. We have a total of 20 living patients (51.3%) and 19 deceased patients (48.7%) except those lost to follow-up after the 4.5-year assessment.

Group A" was found to represent 12 patients (30.8%) of which 8 patients (20.5%) were alive and 4 patients (10.3%) had died. Group B" had 2 alive and 1 deceased. On the other hand, group C" contained 24 patients (61.2%) including 10 living patients (26.3%) and 14 deceased patients (36.8%).

The patients are represented in number in their different prognosis groups after integration of P001. The difference between the deaths of groups A" and C" is significant with $p = 0.01$.

Table 1. Become of patients in their different groups by plasma cell morphology algorithm modified by the integration of P101 and P001.

Groups	Alive	Lost to Follow up	Deceased	Total in number
A"	8	10	4	22
B"	2	2	1	5
C"	10	8	14	32
Total	20	20	19	59

Table 2. Alive and deceased with the formulas integrating the plasma cell P001.

Groups	Alive	Deceased	Total
A"	8	4	12
B"	2	1	3
C"	10	14	24
Total	20	19	39

Legend: ISS Stages = Prognostic Stages of the International Staging System; PMA groups = MM prognosis groups by plasma cell morphology algorithm.

5. Discussion

The prognosis of multiple myeloma by PMA, and the choice of the therapy to be implemented, firstly involves the enumeration of the types of plasma cells present in the patient, and the integration of the majority of plasma cells in number in the Goasguen' formulas prognostic groups while taking into account their specific effects on early death.

5.1. Types of Plasma Cells According to the Morphology Algorithm of GOASGUEN

The most common plasma cell types were the same as in MUFUTA's study [1]. They were in the following decrease order: mature plasma cells (P000), aberrant plasma cells (P001), proplasmocytes I (P100), and immature plasma cells (P101), which together made up 96.7% of plasma cells as shown in **Figure 1**. The other remaining types (P110, P011, P010 and P111) were only 3.3%.

The rate of aberrant plasma cells (P001) and the rate of immature plasma cells (P101) were very high and represented the second and fourth ranks in number of plasma cells.

It is known that the plasmoblast (P111) is an independent element of poor prognosis at the level ≥ 2% [3] [4]. In this work, the plasmoblast was found at the level ≥ 2% in six (10.2%) patients, it varied between 3% and 18.2%.

The rate of aberrant plasma cells (P001) higher than that of mature plasma cells (P000) was found in our studies in 22% of patients and was determinant in increasing the number of patients in group C with a poor prognosis.

The set of plasmoblast (P111), proplasmocyte I (P100), proplasmocyte II (P110) and mature plasma cell (P000) which was most observed by GOASGUEN in the Caucasian population at 93% represented only 71.7% in our patients [2]. Our results differed from those in the literature [2], but were consistent with our previous study on Plasma cell morphology in multiple myeloma.

Our results on the plasmoblast were consistent with certain observations in the literature, where the level of plasmoblast greater than or equal to 2% was observed in 8% - 15% of patients [3] [4].

This level of aberrant plasma cells (P001) higher than that of mature plasma cells (P000) was 10% - 15% with ZANDECKI [2] and 32.4% in our previous work [1]. In Angers, this rate was considered negligible.

5.2. Prognosis According to the GOASGUEN Formulas

It should be noted that only 71.7% of the plasma cells of our patients could be integrated into the prognosis formulas of GOASGUEN. From the four types of plasma cells most commonly encountered in us, only two types of plasma cells P000 and P100 were included in Goasguen's prognosis formulas which included four types of plasma cells which represented 93% of plasma cells in Caucasians according to GOASGUEN [2]. However, our study population presented certain peculiarities, including the high number of immature and/or aberrant plasma cells encountered in more than 26.6% of cases, but not taken up by Goasguen's formulas. This meant that these Goasguen's formulas in their current original forms did not seem suitable for our patients because they were limited by the plasma cell types that composed them.

5.3. Prognosis after Integration of Immature P101 Plasma Cells

The original prognosis formulas did not take into account the plasma cell P101,

to know the prognosis of patients with a high number of P101, we integrated them into the group formulas.

It is well known that the poor responders were patients with immature plasma cells, including the group with P111 ≥ 2%. The number of poor responders must be equal to the number of plasmoblast myelomas, increased by patients with P000 < 66% and P100 less than the number of immaturity plasma cells integrated and/or not integrated in the previous formulas.

The integration of plasma cells with the characteristics of immaturity P101 in the formulas of the groups had made it possible to modify the formulas of the second group and of the third group.

The new results observed had shown that group A became A', in this case was not concerned by the plasma cell immaturity of P101. Therefore, it remained unchanged with 32 patients (54.2%). The two groups affected by the immaturity of P101 were group B' and group C'. Thus, group B' henceforth had been reduced to 13 patients (22%). The C' group with a poor prognosis was now increased by the presence of immature P101 plasma cells. The number of his patients had risen to 14 (23.7%) as can be seen in **Figure 2**.

5.4. Impact and Significance of P001 ≥ 15% on the Prognosis Established with P101

The becoming of the patients observed by counting the number of deaths before 18 months, had shown us that there were 8 deaths in the first group A', 3 deaths in the second group B' and 6 deaths in the third group C'. This gave a total of 17 deaths within 18 months.

Examination of the plasma cell types in deceased individuals from these three prognostic groups showed that 14 of the 17 people had in common a P001 plasma cell level ≥ 15% of the plasma cells encountered. Which made 82.4% of deaths in 18 months and 23.7% of total patients. These were 5 deaths from the first group A', 3 deaths from the second group B' and 6 deaths from the third group C'. However, only 2 people with less than 15% P001 had died within 18 months of diagnosis. This made only 11.8% of deaths.

This finding of 82.4% of the patients who had a short survival, whatever the group, showed that they had in common a level of P001 ≥ 15% of the patient's plasma cells. Thus, we considered the plasma cell P001 level ≥ 15% to be an element linked to early death.

In this study, we had 29 patients with P001 ≥ 15% and 30 patients with P001 ≤ 15%. In the last 30 patients group, there were only 3 deaths in which 2 of them had died within 16 months and one at 38 months.

From the above, we found that the level of P001 ≥ 15% regardless of the group was an independent factor of poor prognosis as is P111 ≥ 2%.

5.5. Integration of P001 in the Formulas of the Prognosis Groups

Thus, given the number of P001 and the influence of P001 ≥ 15% on death, it became mandatory to include P001 in the formulas of the prognosis groups. The

final formulas were those which integrated P101 and P001 and took into account P001 ≥ 15% as an independent factor of poor prognosis.

The high number of patients observed in the group with poor prognosis, now named group C", which represented more than half of the patients, and the number of deaths in this group clearly showed that this third group C" was really a group of bad responding. This seemed to explain the aggressive character known in multiple myeloma in Black subjects. This character was evoked in Ivory Coast in a clinical study, Koffi attributed it to the delay of diagnosis [5]. While in Mali, Diallo explained it by a long average consultation time [6]. This trait was also observed among Blacks in the United States of America [7].

In view of these results, by following the distribution of patients into new groups, we clearly noted that at the time of diagnosis, taking into account the PMA from Goasguen, the prognosis group formulas of which were modified by the integration of P101, P001 and the demonstrated influence of the plasma cell P001 ≥ 15%, element of poor prognosis, we found ourselves with a different distribution of patients into prognosis groups dominated by the high number of patients in the group C", this is a poor prognosis, as seen in **Figure 2**.

This study allowed us to observe that, the aggressive character of the MM of the Black subject was linked to the importance of the plasma cell immaturity of P101, to the importance of the presence of the aberrant plasma cells P001 and especially to the emergence of these aberrant plasma cells P001 at the rate ≥ 15%.

The advantage of the modified formulas is that apart from the patients of the other groups, the patients of group C" of poor responders, who had a real survival greater than 30 - 46 months, are those who received treatment alternative to the usual treatment with Melphalan-Prednisone. This showed the interest there is in looking for the prognosis group of patients according to the doubly modified formulas, based on the PMA integrating aberrant plasma cells and immature plasma cells, taking into account their specific effects on early death in the choice of the most suitable therapy for the patient.

5.6. Patient Survival

Survival was characterized by life and death. The survival analysis does not concern those lost follow-up, who were however numerous at 20 (33.9%). Thus, the living and the deceased are represented in **Table 2**, divided into their different prognosis groups established after the integration of P101 and P001 and the effects of P001 ≥ 15% taken into account.

The death rate in group C" was found to be greater than the death rate in group A" and group B". This gave a statistically significant difference of $p = 0.01$ between group A" and group C" on death.

6. Conclusions

Characteristics, plasma cell counts, and vitamin D levels in Congolese patients with MM, demonstrate why MM is an aggressive disease in Blacks compared to the Caucasian population.

The prognosis by PMA according to the definitive formulas established with P101 and P001, taking into account the weight of P001 ≥ 15% on death, is more efficient than the prognosis by the ISS method.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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