Cytochemical, Functional, and Proliferative Characteristics of Promonocytes and Monocytes From Patients With Monocytic Leukemia

By Ralph van Furth and Theda L. van Zwet

This article deals with a prospective study on the cytochemical, functional, and proliferative characteristics of promonocytes and bone marrow and peripheral blood monocytes of 20 patients with acute monocytic leukemia and 7 patients with chronic monocytic leukemia. The results show a wide variation in the peroxidase and esterase activities in these cells, whereas the percentages of mononuclear phagocytes with Fcγ and C3b receptors did not differ appreciably from those in normal individuals. A discriminant analysis of these data and corresponding data from normal individuals showed that a below-normal peroxidase activity of circulating monocytes has predictive value for the presence of monocytic leukemia; a below-normal esterase activity has less, but nevertheless some, predictive value in this respect. An increase in the percent-age of circulating monocytes, a decrease in the percentage of Fcγ or C3b receptors, and a decline in the ability to phagocytose bacteria has no predictive value for the presence of monocytic leukemia. The mean percentage of patients' promonocytes that incorporated ³H-thymidine amounted to 80.9%, which is close to the control value in normal individuals. The mean values for the labeling indices of cultured bone marrow and peripheral blood monocytes are 1.0% and 0.74%, respectively; when ³H-thymidine was added to whole blood, the labeling index of the monocytes amounted to 3.6%. These percentages are only a little higher than those found for monocytes of normal individu-als. These results indicate that the majority of the circulating monocytes in acute and chronic monocytic leukemia are not actively dividing or blast cells.

Mononuclear phagocytes constitute a cell line that originates in the bone marrow with the monoblast. After division, the monoblast forms two promonocytes, which in turn divide and give rise to two monocytes. Monocytes leave the bone marrow, are transported by the circulating blood, and migrate to the tissues, where they differentiate into macrophages. The origin, kinetics, and characteristics of the mononuclear phagocytes have been studied extensively in animals and to a limited extent also in healthy individuals.

Each hematopoietic cell line can become leukemic, and two forms of true monocytic leukemia, i.e., acute monocytic leukemia (AMoL) and chronic monocytic leukemia (CMoL), and one mixed form, acute myelomonocytic leukemia (AMmL), are known. In the acute forms of leukemia, the circulating cells are usually considered to be more immature than similar circulating cells in normal individuals and are often called monoblasts. However, this involves an assumption whose validity requires demonstration. An attempt was therefore made to determine various characteristics of mononuclear phagocytes in a prospective study in patients suffering from monocytic leukemia. In the present report, the findings concerning the cytochemical, functional, and proliferative characteristics of bone marrow and circulating mononuclear phagocytes from patients with AMoL and CMoL are described and discussed in relation to results obtained earlier for corresponding cells from normal individuals.

MATERIALS AND METHODS

Patients

Twenty patients with AMoL and seven patients with CMoL were studied between 1973 and 1981. The diagnosis was based on the clinical picture and the number of blood monocytes above 0.86 x 10⁹/liter (i.e., the mean number plus twice the standard deviation in healthy individuals; Table 1), as well as the morphology and cytochemistry of the circulating blood monocytes. The bone marrow also showed an increase in the number of monocytes and their precursor cells (Laboratory of Haematopathology, Dr. P. Lopes Cardozo). Cases of myelomonocytic leukemia were not included in this study. The total numbers of leukocytes and monocytes at the time of blood and bone marrow sampling are given in Table 1. All patients were studied before chemotherapy was instituted.

Preparation of Bone Marrow Cell Suspensions

Preparations of mononuclear cells from bone marrow were made from aspiration samples obtained by sternal puncture or from biopsy specimens from the iliac crest. The methods used to obtain cell suspensions for cytocentrifuge preparations and culture have been described in detail elsewhere. After these procedures, the cells were suspended in culture medium (see below) to a concentration of 6.0-8.0 x 10⁹ mononuclear phagocytes (i.e., promonocytes and monocytes) per milliliter.

Preparation of Blood Monocytes

The preparation of blood monocyte suspensions has been described in detail elsewhere. Monocytes were obtained from venous blood collected in 20 U/ml heparin. A monocyte-lymphocyte-rich suspension was prepared by density centrifugation of blood
PROMONOCYTES AND MONOCYTES IN M.OL. 299

Table 1. Total Numbers of Peripheral Blood Monocytes of Patients With AMoL and CMoL.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total Number of Leukocytes (10^6/Liter)</th>
<th>Percentage of Monocytes (%)</th>
<th>Total Number of Monocytes (10^6/Liter)</th>
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<tbody>
<tr>
<td>AMoL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.95</td>
<td>32</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>8.5</td>
<td>16</td>
<td>1.4</td>
</tr>
<tr>
<td>3</td>
<td>6.0</td>
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</tr>
<tr>
<td>4</td>
<td>4.7</td>
<td>54</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>10.7</td>
<td>40</td>
<td>4.3</td>
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<tr>
<td>6</td>
<td>5.5</td>
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<tr>
<td>7</td>
<td>20.3</td>
<td>27</td>
<td>6.1</td>
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<tr>
<td>8</td>
<td>7.1</td>
<td>96</td>
<td>6.3</td>
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<tr>
<td>9</td>
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<td>8.9</td>
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<td>18</td>
<td>120.0</td>
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<td>19</td>
<td>118.4</td>
<td>95</td>
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<tr>
<td>20</td>
<td>300.0</td>
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<tr>
<td>21</td>
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</tr>
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<td>27</td>
<td>71.0</td>
<td>29</td>
<td>20.6</td>
</tr>
<tr>
<td>Normal individuals†</td>
<td>6.8</td>
<td>4.9 ± 1.5</td>
<td>0.34 ± 0.26</td>
</tr>
</tbody>
</table>

*Patients listed according to increasing numbers of monocytes per liter blood.
†Data from reference 5.

on a Ficoll-Isopaque gradient. The interphase layer was collected and washed 3 times with buffered saline containing 0.5 U/ml heparin and suspended in culture medium (see below) to a concentration of 1.0–2.0 x 10^6 monocytes/ml. Blood smears were also made and stained with Giemsa stain for morphological study.

Cell cultures

Suspensions of bone marrow cells were cultured in medium 199 containing 50% (v/v) inactivated newborn calf serum (Grand Island Biological Co., Grand Island, NY) penicillin (2,000 U/ml), and streptomycin (50 μg/ml); peripheral blood mononuclear phagocytes were cultured in the same medium, but with 20% instead of 50% serum. One milliliter of the cell suspension was added to a Leighton tube containing a coverslip (10 x 35 mm) and incubated in an atmosphere of 5% CO2 in air at 37°C for 2 hr. By that time, most of the mononuclear phagocytes had attached to the glass; the supernatant was discarded. After two gentle washes with medium 199 at room temperature, 1 ml medium 199 containing newborn calf serum was added and the cultures were reincubated. Four hours later, the coverslips were washed in medium 199, removed from the tubes, and rapidly air-dried prior to fixation and staining. For the morphological studies, the cells were stained with Giemsa stain.

Cytochemistry

Peroxidase staining was performed according to Kaplow7 with benzidine hydrochloride as substrate, and esterase activity was determined according to Ormstein et al.6 with α-naphthyl butyrate, which is specific for mononuclear phagocytes, as substrate. Both procedures have been described in detail elsewhere.16

Fcγ and C3b Receptors

The presence of Fc receptors was determined with sheep red blood cells coated with specific mouse IgG antibodies (ElgG) and that of C3b receptors with sheep red blood cells coated with specific rabbit IgM antibodies and mouse complement (ElgMC). Both methods have been described in detail elsewhere.1

Phagocytosis

For assessment of the phagocytic activity of mononuclear phagocytes, Staphylococcus epidermidis served as particle and 10% AB serum as opsonin, as described in detail elsewhere.17 In addition, the ingestion of IgG-coated sheep red cells (see above) was assessed.

Pinocytosis

Pinocytic activity was determined with dextran sulfate (mol wt 500,000) as indicator substance.10

In Vitro Labeling With 1H-Thymidine

For in vitro labeling of cells cultured in Leighton tubes, 0.1 μCi/ml 1H-thymidine (specific activity 6.7 Ci/m mole; New England Nuclear Corp., Boston, MA) was added to the medium, and after 6 hr of incubation, the cells were carefully washed, fixed in absolute methanol, and dried. Labeling of monocytes in whole blood was done by adding 0.1 μCi 1H-thymidine to 1 ml heparinized blood in a sterile plastic test tube (Falcon, Becton Dickinson, Amersfoort, The Netherlands), and after 2 hr of incubation at 37°C, a blood sample was spun down in a microhematocrit centrifuge, smears were made from the buffy coat, the cells were fixed in absolute methanol and dried. Autoradiography was performed as described previously.7 Since the background radioactivity did not exceed 5 grains/cell area, all cells with more than 5 grains overlying the nucleus were considered positive.

Statistical Analysis

For statistical analysis of the data, use was made of multiple regression analysis and the results expressed as correlation coefficient (r) and the p value for regression. In the tables and figures, the data of normal individuals are presented as mean values (± 1 SD). Values lying within the range of the mean value ± 2 SD were considered normal.

General Remarks

The morphological criteria used to characterize a cell as a promonocyte or monocyte have been described.7 The data on the characteristics of bone marrow promonocytes and monocytes and blood monocytes of normal individuals derive from an earlier study in which the same techniques were used,1 and these data were supplemented with data on peripheral blood monocytes obtained in six healthy subjects investigated in 1981. These two sets of data showed no divergence.

Because in the early period of this study (up to 1975), all of the necessary techniques had not yet been operationalized, all of the characteristics could not be studied in bone marrow and blood
samples from all of the patients. Furthermore, it was not always possible to determine all of the characteristics of bone marrow mononuclear phagocytes, because in some cases, so many cells became detached from the glass that too little material was available.

RESULTS

Promonocytes and Bone Marrow Monocytes

Cell Ratio

The ratio between the monocytes and other mononuclear phagocytes (i.e., monoblasts plus promonocytes) was determined in 6-hr bone marrow cultures; differentiation between monoblasts and promonocytes could not be made with certainty in Giemsa-stained preparations. For patients with AMoL, the mean ratio was 94.9:5.1 and for patients with CMoL 93.0:7.0. These values do not differ from the monocyte-to-promonoocyte ratio of 94.8:5.2 found in normal individuals.

Cytochemistry

In about two-thirds of the patients, the percentage of esterase-positive promonocytes and monocytes lay in the normal range; a small number of the patients had only a very low percentage of positive cells (Fig. 1). The latter group had equal numbers of cases of AMoL and CMoL.

The percentage of peroxidase-positive promonocytes and monocytes varied widely among the patients with AMoL and CMoL. Only five patients had normal values, and four of these had CMoL. In three of the latter patients, less than 10% of the cells were positive (Fig. 1).

Receptors

A lower than normal percentage of promonocytes and monocytes with Fcγ receptors was only found in 2 of 10 patients (Fig. 2, Table 2). The percentage of bone marrow monocytes with C3b receptors was similar to that in healthy individuals or higher, except in one case; for the promonocytes, these values varied (Fig. 2, Table 2).

Endocytosis

The phagocytic activity of promonocytes, as studied with opsonized Staphylococcus epidermidis, was normal in the majority of cases (Fig. 3), and the exceptions were equally distributed over the AMoL and CMoL groups. The phagocytosis of opsonized sheep red cells (ElG) by promonocytes was slightly reduced in the majority of the patients with AMoL and CMoL (Table 2). The ingestion of complement-coated red cells (ElgMC) by promonocytes from patients with AMoL was of the same order as that in the controls (Table 3).

Normal or increased phagocytic activity of bone marrow monocytes with respect to opsonized Staphylococcus epidermidis was found in all but three patients (Fig. 3). Phagocytosis of ElgG by these cells was only reduced in patients with CMoL (Table 2); in the AMoL patients, the phagocytosis of ElgMC was similar to that in the controls (Table 3).

The pinocytic activity of promonocytes and monocytes varied greatly (Fig. 3); reliable values for promonocytes were only obtained in five cases, because a large proportion of the cells of the other subjects...
Fig. 2. Receptors for Fcγ and C3b on the membrane of promonocytes and bone marrow and peripheral blood monocytes of patients with AMoL and CMoL. The individual values indicate the percentage of positive cells; the hatched area represents the normal values (see legend Fig. 1).

Table 2. Phagocytosis of IgG-Coated Red Cells by Promonocytes and Bone Marrow and Blood Monocytes

<table>
<thead>
<tr>
<th>Patients</th>
<th>Promonocytes</th>
<th>Bone Marrow</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Attached</td>
<td>Ingested</td>
<td>Attached</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>AMoL</td>
<td>16.6 ± 17.4</td>
<td>73.7 ± 23.2</td>
<td>90.3 ± 15.3</td>
</tr>
<tr>
<td>CMoL</td>
<td>6.5</td>
<td>82.5</td>
<td>89</td>
</tr>
<tr>
<td>Normal</td>
<td>0.0</td>
<td>97.6 ± 5.1</td>
<td>97.6 ± 5.1</td>
</tr>
</tbody>
</table>

*From reference 5.

Fig. 3. Phagocytosis of Staphylococcus epidermidis and pinocytic activity shown by promonocytes and bone marrow and peripheral blood monocytes of patients with AMoL and CMoL. The individual values indicate the percentage of positive cells; the hatched area represents the normal values (see legend Fig. 1).
became detached during incubation with dextran sulfate.

3Thymidine Labeling

The percentage of promonocytes labeled after incubation with 3H-thymidine lay within or slightly above the upper limit of the normal range except in one case (Fig. 4). The calculated mean value of 80.9% ± 18.2% (n = 10) does not differ significantly from that found for normal individuals (i.e., 78.8% ± 7.7%). The percentage of labeled bone marrow monocytes was 3% or lower, with a mean value of 1.0% ± 0.9% (n = 11) (Fig. 4); in normal individuals this value was 0.1.

Peripheral Blood Monocytes

Cytchemistry

The percentage of esterase-positive monocytes showed very marked variation, and in half of the cases 3H-THYMIDINE LABELING was lower than the normal value (97.0% ± 3.3%) (Fig. 1); the high and low values were equally distributed over the AMoL and CMoL groups.

The percentage of peroxidase-positive monocytes lay in the normal range of 94.3% ± 5.9% (Fig. 1) in only 7 of 25 patients with AMoL or CMoL; all of the others had lower values, in 4 cases even lower than 5%, and 2 of these patients even had monocytes with no peroxidase-positive granules. In all cases with a decrease of peroxidase-positive monocytes, the granulocytes were peroxidase positive, which indicates that these patients did not have a myeloperoxidase deficiency.

Receptors

Fcγ and C3b receptors were found in the great majority of the monocytes of patients with AMoL or CMoL; there were only four exceptions (Fig. 2, Tables 2 and 3). Lower values were equally distributed over the patients with AMoL and CMoL.

Endocytosis

Opsonized Staphylococcus epidermidis were phagocytized by more than 90% of the monocytes in 19 out of 26 cases (Fig. 3). Lower values were equally distributed over the patients with AMoL and CMoL. The ingestion of IgG by monocytes was on a slightly lower level in these patients than in healthy individuals (Table 2), and the ingestion of IgMC was on a slightly higher level in patients with AMoL than in the controls; the mean values for the patients with CMoL and the normal controls were roughly the same (Table 3).

Pinocytic activity was normal or increased in the majority of the cases and showed only moderately decreased values in 3 of 21 cases (Fig. 3).

3H-Thymidine Labeling

The labeling index of cultured peripheral blood monocytes lay between 0% and 1.0% in 13 of the 17 cases, in 3 cases between 1.0% and 2.0%, and in 1 case this value was 5.5% (Fig. 4). The mean labeling index was 0.74% ± 1.3% (n = 17), which does not differ

![Fig. 4. In vitro 3H-thymidine labeling of bone marrow promonocytes and monocytes and peripheral blood monocytes of patients with AMoL and CMoL; the hatched area represents the normal values (see Fig. 1).](image-url)
significantly from the value of 0.1% ± 0.2% found for peripheral blood monocytes from healthy donors. The labeling index in whole blood preparations of patients with AMoL or CMoL was 3.6% ± 3.6% (n = 20); in healthy individuals this value was 1.1% ± 0.7%.

**Statistical Analysis**

For various characteristics, the correlation between or within the various types of cell (i.e., bone marrow promonocytes, bone marrow monocytes, and blood monocytes) was investigated (Table 4). The cytochemical characteristics showed good correlations. The peroxidase activity of all cell types showed good correlation (r values ranging from 0.77 to 0.88). For the esterase activity of bone marrow promonocytes and monocytes, the correlation coefficient amounted to 0.95; between bone marrow promonocytes and blood monocytes this coefficient was 0.60 and a weak correlation (r = 0.35) was found between bone marrow and blood monocytes. Weak correlations were found for the receptors and the functional activities of the various cell types, possibly due to the small variance between the values for these characteristics, which impedes correlation analysis within each type of mononuclear phagocyte.

**DISCUSSION**

The main conclusions to be drawn from the present study are as follows. The cytochemical characteristics of promonocytes and monocytes from patients with AMoL and CMoL showed considerable variation, which is not the case for healthy individuals; in the majority of the patients, however, the values for membrane receptors and functional characteristics lay within the normal range. The mean 3H-thymidine labeling indices of the patients' promonocytes and monocytes did not differ very much from the value found for healthy individuals. These findings indicate that mononuclear phagocytes from AMoL and CMoL patients can function normally, even though their cytochemical characteristics are abnormal. A similar conclusion could be drawn from an earlier study in which use was made of a different method to measure the phagocytosis and intracellular killing by peripheral blood monocytes obtained from patients with AMoL or CMoL.12

For the characteristics of circulating blood monocytes of patients with AMoL and CMoL under study, a discriminant analysis was performed relative to the corresponding characteristics of blood monocytes of healthy individuals. The results show that a below-normal percentage of peroxidase-positive monocytes has a predictive value of 0.70 (p < 0.001) for disease, and the predictive value of below-normal esterase activity is much lower (r = 0.31, p < 0.1), whereas an increase in the percentage of circulating blood monocytes (r = 0.13, p > 0.1), a decrease in the percentage of monocytes with Fc-y receptors (r = 0.1, p > 0.1) or C3b receptors (r = 0.5, p > 0.1), and a decline in the capacity to phagocytose bacteria (r = 0.15, p > 0.1) is not predictive at all.

The present findings are relevant for the diagnosis of leukemia. The occurrence in the blood of esterase-negative or peroxidase-negative cells with the morphology of monocytes does not mean that these cells are not monocytes, but suggests the presence of monocytic leukemia.

Earlier studies were concerned with only a limited number of the cytochemical, membrane, functional, and proliferative characteristics, and often only qualitative data were reported; in particular, none of these reports provided quantitative data for a large group of patients. Therefore, comparison with the quantitative data obtained in this prospective study is not possible.

The 3H-thymidine labeling index of the monocytes of the bone marrow and peripheral blood was, with only a few exceptions, very low. From this very low labeling index of the circulating monocytes in acute and chronic monocytic leukemia, it must be concluded that only a small number of dividing mononuclear phagocytes circulate in the blood. Immature cells are

<table>
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<tr>
<th>Characteristics of Cells</th>
<th>Promonocytes Versus Bone Marrow Monocytes</th>
<th>Promonocytes Versus Blood Monocytes</th>
<th>Bone Marrow Monocytes Versus Blood Monocytes</th>
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</thead>
<tbody>
<tr>
<td>Peroxidase</td>
<td>15 0.88 &lt;0.001</td>
<td>15 0.77 &lt;0.001</td>
<td>15 0.82 &lt;0.001</td>
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<td>Esterase</td>
<td>15 0.95 &lt;0.001</td>
<td>14 0.60 &lt;0.01</td>
<td>14 0.35 &lt;0.10</td>
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<td>Fc-y receptor</td>
<td>9 0.60 &lt;0.1</td>
<td>9 0.02 &gt;0.75</td>
<td>10 0.75 &lt;0.025</td>
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<td>C3b receptor</td>
<td>6 0.20 &gt;0.5</td>
<td>6 0.25 &gt;0.75</td>
<td>8 0.52 &lt;0.10</td>
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<td>Ingestion of S. epidermidis</td>
<td>16 0.85 &lt;0.001</td>
<td>16 0.11 &gt;0.75</td>
<td>16 0.10 &gt;0.75</td>
</tr>
</tbody>
</table>

*Correlation coefficients were calculated for the percentage positive cells with the peroxidase activity, esterase activity, Fc-y receptors, C3b receptors, and ingestion of S. epidermidis.

n, Number of determinations; r, correlation coefficient; p, p value for regression.
called blast cells by hematologists on the basis of morphological characteristics of the nucleus and the cytoplasm. In this sense, the term monoblast is also applied to cells in the peripheral blood of patients with monocytic leukemia. Cell biologists and others correctly reserve the term blast cell for cells that divide, and apply not only morphological but also other characteristics (e.g., DNA synthesis and proliferative capacity in vitro) for the classification of a cell as a dividing cell. From the present study, in which the incorporation of $^3$H-thymidine was studied, it is evident that the proliferative activity of the monocyte population is very low. On these grounds it would be preferable to avoid using the term monoblast to denote the proliferative activity of the monocyte. From the present study, in which the incorporation of $^3$H-thymidine was studied, it is evident that the proliferative activity of the monocyte population is very low. On these grounds it would be preferable to avoid using the term monoblast to denote the proliferative activity of the monocyte except when there is solid evidence that a large percentage of these circulating monocytes are dividing cells.

With respect to the increased number of mononuclear phagocytes in the tissues of patients with AMoL or CMoL, an interesting point concerns the question of how these mononuclear phagocytes have accumulated at that site, i.e., whether they show increased numbers because more cells have left the circulation randomly and migrated to the tissues, where they become macrophages, or have proliferated locally, i.e., by division of mononuclear phagocytes already present in or recruited to a tissue site. Since the number of circulating monocytes is increased in monocytic leukemia, an increase in the number of cells migrating to the tissues would be expected and this would lead to an increase in the number of macrophages in various organs (e.g., the liver). In all probability, the relatively small number of DNA-synthesizing mononuclear phagocytes among the migrating monocytes divide in the tissues, but their contribution to the increased number of tissue macrophages must be relatively small. Whether these DNA-synthesizing cells are monoblasts or promonocytes or more mature cells of the mononuclear phagocyte cell line is uncertain, but this problem can be approached by the use of electron microscopy.

ACKNOWLEDGMENT

The help of Dr. P. C. J. Leijh in the evaluation of the results is gratefully acknowledged. The authors are grateful to the staff of the Department of Clinical Haematology for allowing them to study the patients with acute or chronic monocytic leukemia.

REFERENCES

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