Characterization of B-Cell Leukemias: A Tentative Immunomorphological Scheme

By Benjamin Koziner, Sanford Kempin, Sharon Passe, Timothy Gee, Robert A. Good, and Bayard D. Clarkson

Analysis of the morphological and immunologic [surface (Sm Ig) and cytoplasmic (Cy Ig) immunoglobulin, faintness (f.imfl)] or brightness (b.imfl) of surface immunofluorescence, rosette formation with mouse erythrocytes (MR), or sheep red cells coated with C3 (EAC) characteristics of the neoplastic lymphocytes involved in 137 cases of B-cell leukemias allowed the differentiation of the following cytologic categories: B1 small lymphocyte (71): Sm Ig+, f.imfl., Cy Ig−, MR−, EAC−; B2 prolymphocyte (4): Sm Ig+, f.imfl., Cy Ig−, MR−, EAC+; B3 plasmacytoid lymphocyte (2): Sm Ig+, b.imfl., Cy Ig−, MR−, EAC±. B4 small cleaved lymphocyte (23): Sm Ig+, b.imfl., Cy Ig−, MR−, EAC−. B5a large cleaved and B5b noncleaved lymphocytes (14): Sm Ig+, f.imfl., Cy Ig−, MR−, EAC−. B6 small noncleaved "Burkitt-like" lymphocytes (5): Sm Ig+, b.imfl., Cy Ig−, MR−, EAC−. B7 plasma cell (2): Sm Ig−, Cy Ig±, MR−, EAC−. B8 hairy cell (16): Sm Ig+, b.imfl., Cy Ig−, MR−, EAC−, also exhibiting ingestion or attachment of particulate material, not seen in other types. Improved delineation of the heterogeneous group of B-cell leukemias might be of developmental significance in lymphocyte differentiation and improve current prognostic and therapeutic criteria.

Despite their variable morphological expression and clinical behavior, most adult malignant lymphomas and leukemias belong to the B-cell lineage. Cell marker analysis has allowed a better categorization of these disorders of clinical and developmental significance.1-8

We have previously reported on the differences in surface marker characteristics when comparing the neoplastic cells in chronic lymphocytic leukemia (CLL) and other B-cell leukemias.5 In CLL, the cells involved are predominantly monoclonal B-lymphocytes which display faint immunofluorescence and high frequency avidity for mouse erythrocytes. Conversely, in most other types of B-cell leukemias, the neoplastic cells lack receptors for mouse erythrocytes, usually exhibiting more abundant surface immunofluorescence.

In this article we extend these observations and further dissect the B-cell leukemias according to their surface phenotypes and morphological features. This type of analysis provides a useful approach to the objective diagnosis and classification of B-cell neoplasias, and make it possible to learn further about the process of differentiation of normal and neoplastic B lymphocytes.

MATERIALS AND METHODS

Patient Population

One-hundred and thirty-seven adult patients with various types of B-cell leukemias were seen at the Hematology/Lymphoma Service of Memorial Hospital since 1976. All patients had active leukemia at the time of the study and were either previously untreated or relapsing after therapy. Although a majority of patients had leukemic cell counts above 10,000 cells/mm3 some had lower numbers but with a predominance of leukemic elements.

The morphological features of the leukemic cells were assessed on standard trichrome-stained smears of peripheral blood (PB) and bone marrow (BM), and permanent preparations of rosetting cells made in a cytospin (Cytospin, Shandon Southern, Pa.). Cytologic characterization of the neoplastic cells was carried out essentially following the taxonomic scheme and terminology proposed by Lukes and Collins.9

Surface Marker Studies

The mononuclear cells were separated from heparinized PB and BM by isopycnic centrifugation.10 Viability by Trypan blue dye exclusion always exceeded 90%. Phagocytic cells were identified by incubation of 5–10 × 106 mononuclear cells for 1 hr with 0.8 μ polystyrene particles on the same cellular preparations employed for surface marker analysis.

Lymphocytic preparation and immunofluorescent staining were performed as previously reported.3 A polyvalent rabbit antiserum to human immunoglobulin (nl = 13% ± 6%, mean ± 1 standard deviation) and antisera specific for gamma, mu, alpha, delta, kappa, and lambda light chains were used. Fluorescein conjugated F(ab')2 fragments of specific antisera to gamma (nl = 1.5 ± 1%), mu (nl = 7% ± 5%), alpha (nl = 2% ± 1%), and delta (nl = 4% ± 3%) heavy chains were purchased from Kallestad Laboratories (Chaska, Minn.). Indirect binding of aggregated IgG was performed as reported by Dickler et al11 (nl = 14% ± 6%). The cells were examined with a Leitz Ortholux microscope equipped with vertical fluorescent illumination. A minimum of 200 cells were counted per slide. For the determination of intracytoplasmic immunoglobulin, smears were made using a cytospin and stored at −70°C before use. Smears were subsequently fixed on ice-cold ethanol (95%) containing acetic acid (5%), washed in phosphate-buffered saline (PBS), and later stained with the fluorescein-conjugated anti-human F(ab')2 immunoglobulin reagents. After washing with PBS, the slides were sealed and examined by immunofluorescence.

Rosette formation with mouse erythrocytes was carried out as previously described.7 Normal value in controls is 5% ± 3%. The

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Table 1. B-Cell Leukemias: Summary of Cell Marker Findings

<table>
<thead>
<tr>
<th>Type</th>
<th>Surface Immunoglobulin</th>
<th>Cytoplasmic Immunoglobulin</th>
<th>Mouse Rosette (Mean %)</th>
<th>Complement Rosette (Mean %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>+</td>
<td></td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>(ring)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>+ ++</td>
<td></td>
<td>45</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>(ring)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td>+ ++</td>
<td>±</td>
<td>(1.21)*</td>
<td>(20)*</td>
</tr>
<tr>
<td></td>
<td>(ring)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B4</td>
<td>+ + +</td>
<td></td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>(ring)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B5</td>
<td>+ + +</td>
<td></td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>(ring)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B6</td>
<td>+ + +</td>
<td></td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>(dots)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B7</td>
<td>–</td>
<td></td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B8</td>
<td>+ + +</td>
<td></td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(caps)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal controls (mean %) 5 6

+ to + + +: Intensity of surface immunofluorescence.

*Individual values (only 2 patients were studied).
Fig. 1. Morphological characterization of the different subtypes of B-cell leukemias. B1, small lymphocyte; B2, prolymphocyte; B3, plasmacytoid lymphocyte; B4, small cleaved lymphocyte; B5a, large cleaved and B5b, noncleaved lymphocyte; B6, small noncleaved “Burkitt-like” lymphocyte; B7, plasma cell; and B8, hairy cell.
Table 2. Incidence of Different Surface Immunoglobulin Patterns According to B-Cell Subtypes

<table>
<thead>
<tr>
<th>Surface Immunoglobulin</th>
<th>B-Cell Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B1</td>
</tr>
<tr>
<td>IgM Kappa</td>
<td>17</td>
</tr>
<tr>
<td>Lambda</td>
<td>3</td>
</tr>
<tr>
<td>IgD Kappa</td>
<td></td>
</tr>
<tr>
<td>Lambda</td>
<td></td>
</tr>
<tr>
<td>IgG Kappa</td>
<td>1</td>
</tr>
<tr>
<td>Lambda</td>
<td>1</td>
</tr>
<tr>
<td>IgM-D Kappa</td>
<td></td>
</tr>
<tr>
<td>Lambda</td>
<td>6</td>
</tr>
<tr>
<td>IgM-G Kappa</td>
<td>1</td>
</tr>
<tr>
<td>IgM-A Kappa</td>
<td>1</td>
</tr>
<tr>
<td>IgM-D-G Kappa</td>
<td>1</td>
</tr>
<tr>
<td>IgG Kappa</td>
<td></td>
</tr>
<tr>
<td>IgM ?</td>
<td></td>
</tr>
<tr>
<td>Cytoplasmic IgG</td>
<td>Kappa</td>
</tr>
<tr>
<td>Lambda</td>
<td></td>
</tr>
<tr>
<td>No fluorescencevisualized</td>
<td></td>
</tr>
<tr>
<td>Total (137)</td>
<td>71</td>
</tr>
</tbody>
</table>

The predominant surface immunoglobulin persisted on the leukemic cells after short-term culture and repeated washings.

In this series of 71 patients with CLL, the mean percentage of MR-forming cells was 45%, differing significantly from the values described in control subjects (5% ± 3%) ($p < 0.05$). Moreover, statistically significant differences in the percentage of MR were observed when IgM was the predominant heavy chain as compared with other patterns of membrane immunoglobulin or when a paraprotein was detected in the serum ($p < 0.05$, Kruskal-Wallis Test) (Table 4). Mean value of EAC-forming cells for the entire group was 43%.

In 2 instances of “blastic” progression of CLL, despite a change to a “prolymphocytic” morphology, the cells possessed the same surface phenotype as was originally shown to be present. Moreover, in one case presenting de novo with a morphological diagnosis of “lymphosarcoma cell leukemia” (LSCL) suppos-edly the leukemic expression of an underlying malignant lymphoma—surface marker findings were suggestive of an original surface phenotype characteristic of CLL.

B2 Subtype ($Sm$ Ig+; $b$.imfl., Cy Ig-, MR+, EAC+)

Four cases of prolymphocytic leukemia (PL) were included in this category, being characterized at diagnosis by a homogenous population of medium to large lymphocytes with abundant cytoplasm, open nuclear chromatin, and prominent nucleolus. The cells exhibited bright surface immunofluorescence and an...
increased proportion of MR (mean, 45%) and EAC (mean, 28%) forming cells.

B3 Subtype (Sm Ig+, b.imfl., Cy Ig±, MR±, EAC±)

Two patients with a clinical diagnosis of Waldenström’s macroglobulinemia and circulating plasmacytoid lymphocytes in PB were in this category. Both exhibited IgM on the surface, one of kappa and the other of lambda light chain type. Both patients also had an IgM serum paraprotein of the same light chain type to that found on the cell membrane. The proportion of MR-forming cells was 1% and 21%, respectively, in each of the 2 patients. EAC rosette was only analyzed in the latter patient, and the percentage of rosetting cells was 20%.

B4 Subtype (Sm Ig+, b.imfl. Cy Ig−, MR−, EAC+)

Twenty-three patients presented with a predominance of neoplastic cells in PB that were small to intermediate in size, exhibited compact nuclear chromatin and had a cleaved nuclear shape. Twenty of these patients had a histologic diagnosis of malignant lymphoma from morphological examination of lymphoid tissue.

The incidence of different membrane immunoglobulin patterns in these patients is described in Table 3. In occasional cases, different combinations of heavy chains were encountered, including IgD, IgG, and IgA. These immunoglobulins persisted after trypsination, short-term culture, and were demonstrated upon immunofluorescent staining with F(ab')2 reagents. Surface immunofluorescence was bright. The mean value of MR for the entire group was 14%. The mean percentage of EAC-forming cells was 5%.

B6 Subtype (Sm Ig+, b.imfl., Cy Ig−, MR−, EAC−)

Morphologically, the circulating blast cells observed in this group of patients were characteristically intermediate to large, with finely distributed nuclear chromatin, variable nuclear shape, prominent nucleoli, and basophilic cytoplasm with frequent vacuolization. Numerous mitotic figures were frequently observed in the bone marrow. Although three of the patients had a histologic diagnosis consistent with Burkitt’s lymphoma in lymphoid tissue, another patient was diagnosed as having a large cell lymphoma and the fifth one was “unclassifiable” by morphological criteria.

On immunofluorescent examination, the neoplastic cells displayed bright fluorescence with a tendency to exhibit a “dotted” ring pattern. The mean percentages of MR- and EAC-forming cells were low (3% and 8%, respectively).

B7 Subtype (Sm Ig−, Cy Ig+, MR−, EAC−)

In two cases of plasma cell leukemia (PCL), IgG kappa and IgG lambda, respectively, were detected in the cytoplasm but not on the cell surface with our reagents. The cells resembled atypical plasma cells in both bone marrow and peripheral blood. One patient presented de novo as PCL, while the other one represented the leukaemic expression of a previously diagnosed multiple myeloma. Neoplastic cells forming rosettes with mouse erythrocytes or C3-coated red cells were not detected.

B8 Subtype (Sm Ig+, b.imfl., Cy Ig−, MR−, EAC−, Tendency to Attach and/or Ingest Particulate Material)

The “hairy” cell was usually of intermediate size with an eccentric nucleus and evenly distributed chromatin. “Hairy” cytoplasmic projections were characteristic and best recognized on phase-contrast microscopy. The “hairy” cells in 12 of the 14 patients studied were not resistant to tartaric acid after a positive stain for acid phosphatase. A variable number of cells in most cases studied stained positively with alpha-naphthyl acetate esterase and PAS.

The surface immunoglobulin patterns found in 16 cases with HCL are described in Table 2.
ically, 17%, 39%, and 32% (mean values), respectively, of the cells in suspension from PB, BM, and splenic tissues were found either to incorporate or attach particulate material (latex particles). Four cases expressed IgG-lambda immunoglobulin on the cell surface that remained after overnight culture in serum-free medium and was also revealed when surface immunoglobulin was stained with F(ab')2 reagents. The cells in most cases exhibited significant "capping" (polar distribution of surface immunoglobulin) on standard incubation conditions (30 min at 37°C), which was not regularly seen with normal B-cells. The mean proportion of MR-forming cells was low (5%). An increase in the mean percentage of MR was observed after incubation with neuraminidase (24%). Mean value for EAC-forming cells was 7%.

Clinical characterization of the 137 patients is shown in Table 5. No significant differences in regard to sex and age distribution among the groups were detected. At 3 yr, the survival rates for types B1, B4, B5, and B8 were 90%, 63%, 68%, and 80%, respectively. Although the differences among curves were not statistically significant, the prognosis appeared to be the best for the B1 patients. The small number of patients studied in the other groups precluded their inclusion in the analysis. However, the patients in the B6 category—in which survival data was available—had the shortest survival times (patients were dead at 8, 6, 2, and 1 mo). Further follow-up is required to provide better estimates of the true survival rates.

**DISCUSSION**

Neoplastic proliferations of B-cells are heterogeneous in their morphological features, membrane phenotypes, and functional capacities. However, it has been proposed that they represent malignant deviations "frozen" at distinctive stages of development along the line of differentiation of normal B cells. The clonal origin of B-cell neoplasias is suggested by the predominance of cells showing restriction in regard to immunoglobulin class, IgG subclass, and light chain type. Monoclonal proliferations of IgM, IgG combined with IgD, IgD alone, and less frequently, IgG and IgA have been observed in this series and previously reported by others. The detection of more than one type of surface heavy chain on the neoplastic cells could be attributed to intrinsic immunoglobulin expression, reflecting transitional stages in B-cell ontogeny. Current evidence appears to suggest that immunologic differentiation along the B-cell pathway begins at a pre-B-cell stage, as previously suggested by Gatling et al., in which the cell carries cytoplasmic IgM but no surface immunoglobulin. This is followed by increasing density of surface IgM, eventual transition to IgD, and further on, to IgG and IgA with loss of the receptors for mouse erythrocytes and complement. At the end of this developmental sequence, the cell could acquire the property of synthesizing intracytoplasmic immunoglobulin. At this stage, surface immunoglobulin could not be detected by isotypic reagents but could still be identified by idiotypic antisera.

Another explanation for the presence of multiple membrane-bound isotypes in B-cell neoplasias is the binding of immune complexes or anti-IgG antibody to monoclonal surface IgM (rheumatoid factor). However, similar findings in surface immunoglobulin distribution have been observed using pepsin-digested F(ab')2 antisera or trypsinization and short-term culture in serum-free medium to eliminate the possibility of surface binding through an Fc receptor.

Receptors for complement (EAC), particularly C3, heat-aggregated IgG, and mouse erythrocytes (MR) are easily demonstrable in the small lymphocyte (B1) of CLL. The proportion of MR appears to relate to the maturational stage of the B1 cells, since in our series, highest values were found when IgM was the main heavy chain detected. A progressive decline in the proportion of MR was observed as other surface heavy chains appeared. The lowest values were finally expressed in those cases associated with a serum paraprotein of the same isotypes was present on the cell surface. The expression of these surface markers has been found to be independent of the presence or absence of surface immunoglobulin, detected by immunofluorescence, characteristically faint in this cytologic type. This finding may directly relate to the amount of surface immunoglobulin or to the presence of more "buried" immunoglobulin determinants in the membrane of B1 cells.

It has also been observed that both spontaneously and upon clinical response to therapy, the proportion of cells bearing the monoclonal surface immunoglobulin may decrease, with an eventual return to a normal pattern of distribution. Moreover, we have also noted

<table>
<thead>
<tr>
<th>Cytologic Type</th>
<th>No. of Patients</th>
<th>Male/Female Ratio</th>
<th>Median Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>71</td>
<td>36/35</td>
<td>61</td>
</tr>
<tr>
<td>B2</td>
<td>4</td>
<td>4/0</td>
<td>67.5</td>
</tr>
<tr>
<td>B3</td>
<td>2</td>
<td>2/0</td>
<td>57.5</td>
</tr>
<tr>
<td>B4</td>
<td>23</td>
<td>13/10</td>
<td>56</td>
</tr>
<tr>
<td>B5</td>
<td>14</td>
<td>8/6</td>
<td>57</td>
</tr>
<tr>
<td>B6</td>
<td>5</td>
<td>4/1</td>
<td>44</td>
</tr>
<tr>
<td>B7</td>
<td>2</td>
<td>0/2</td>
<td>67.5</td>
</tr>
<tr>
<td>B8</td>
<td>16</td>
<td>13/3</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>137</td>
<td>80/57</td>
<td></td>
</tr>
</tbody>
</table>
in two cases of CLL that despite a more blastic or "prolymphocytic" morphology the cells preserved the original surface phenotype, including faint monoclonal immunofluorescence, and elevated proportion of MR previously described.38

Four patients presented with a leukemia of B-lymphocytes, paucity of lymphadenopathy, and prominent splenomegaly. Distinctly, most of the cells fitted the morphologic description of "prolymphocytes" (B2) as proposed by Galton et al.39 Bright surface immunofluorescence and an increased proportion of mouse rosetting cells were observed in all four cases, combining features of B1 and neoplastic follicular center cells.

Catovsky et al.40 have previously reported on the high proportion of MR in CLL cases. This range was from 31%-95%.40 In LSLC and PL together, only 8 of 36 patients were regarded as positive having more than 30% of MR. All LSLC and PL cases were positive for surface immunoglobulin and the cells had a greater density of surface immunoglobulin than in CLL. Fluorescent intensity was particularly strong in PL.

In Waldenström's macroglobulinemia, a variable proportion of the PB and BM plasmacytoid lymphocytes (B3) display membrane-bound IgM of similar light chain specificity to that of the secreted serum paraprotein.41,42 Moreover, serum paraproteins other than IgM, such as IgG and IgA, have been observed in association with the clinical and morphological features of WM.43-45 As found in our series, the neoplastic cells may display immunoglobulin only on their surface, show both membrane and cytoplasmic immunoglobulin, or exclusively exhibit intracytoplasmic staining for immunoglobulin.41,42

Lennert46 and Lukes and Collins9 have argued that B-cell lymphomas originate from follicular center cells. Separately, they have formulated new taxonomic schemes based on the presumed functional capacities of the involved cells. On the basis of camera lucida observations, Lukes and Collins formulated a morphologic sequence for B-cell lymphomas that they could relate to progressive stages of activation of an original follicular center cell. Recent surface marker studies have confirmed this initial scheme3,8,47 and supported the predictability of the immunologic phenotype on the basis of conventional morphology.48

A higher density of surface immunoglobulin, increased proportion of C3 receptors, and absence of the receptor for mouse erythrocytes have been observed in leukemias with a predominance of small cleaved lymphocytes (B4) of postulated follicular center origin.1,5,49 The presence of bright surface immunofluorescence helps to differentiate this leukemic cellular type from the small lymphocyte type (B1).1,5 In addition, these cells show rapid "capping" (polar distribution) of surface immunoglobulin during incubation at 37°C. Normal B-cells also show this characteristic but B1 cells do not.50

Either by differentiation or activation, the original small cleaved follicular center cell (B4) could acquire larger size and even a noncleaved nuclear morphology.9 On the basis of this interpretation, the term "histiocytic lymphoma" proposed by Rappaport41 for large cell lymphomas has been challenged. In most cases the lymphoid origin of these large cells is unequivocal.6,52 Moreover, different cell types of clinical relevance have been recognized on the basis of distinct cytologic features among the so-called histiocytic lymphomas.53 In our series of B-cell leukemias, despite their different nuclear configuration, the finding of a similar surface phenotype in large cleaved (B5a) and noncleaved (B5b) cells argues in favor of their common follicular center cell origin, as originally suggested by Lukes and Collins.9

The small noncleaved cells5 involved in nonendemic American Burkitt's lymphoma and its leukemic expression, are monoclonal B-lymphocytes of postulated follicular center origin5,54 that exhibit bright and punctate surface immunofluorescence (B6). Cytoplasmic vacuolation is usually prominent.54-56 Leukemic processes showing a predominance of cells with similar morphological and immunologic characteristics but other histologic diagnosis in solid lymphoid tissue were also observed in this series. A high labeling index with tritiated thymidine, increased DNA/RNA cellular content, and elevated titers of serum lactic dehydrogenase are additional features of the rapidly proliferating cells that characterize this group of patients.56

Both cases of plasma cell leukemia in our series had demonstrable monoclonal intracytoplasmic immunoglobulin but no membrane-bound immunoglobulin by immunofluorescence (B7). Although the proportion of B lymphocytes carrying membrane-bound immunoglobulin has been repeatedly observed to be decreased,7,58 the use of anti-idiotypic antisera raised against individual serum M-components enables recognition of a greater proportion of monoclonal B-lymphocytes and plasma cells.26,27

Despite its well recognized clinicopathologic characteristics,59 considerable controversy continues concerning the origin of the neoplastic hairy cell (B8). In most reported cases, as well as in our own experience, the presence of monoclonal surface immunoglobulin argues in favor of a B-cell origin.60 However, the cell's phagocytic properties61 (whether the hairy cell is actually able to incorporate particulate material into
the cytoplasm or just attach and engulf the material in-between the cytoplasmic projections remains controversial, and cannot be resolved with the methodology employed) and electron microscopic appearance are suggestive of a monocytic lineage. A hybrid cell, with properties of both B-lymphocyte and monocyte, remains as an alternative explanation. Moreover, the hairy cell may reflect an exceptional stage of development or a neoplastic form akin to a normal cell in the bone marrow and/or the spleen.

The present study confirms the phenotypic heterogeneity of B-cell leukemias and supports the concept originally proposed by Lukes and Collins that the correlation of cell marker analysis with the various morphological expressions of B-cell neoplasia is of clinical relevance. Moreover, the information provided by this type of approach appears to be of developmental significance in contributing to define the maturation sequence of B cells.

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CHARACTERIZATION OF B-CELL LEUKEMIAS


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