Suppression of Juvenile Chronic Myelogenous Leukemia Colony Growth by Interleukin-1 Receptor Antagonist

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Bone marrow (BM) and peripheral blood (PB) cells from patients with juvenile chronic myelogenous leukemia (JCML) exhibit spontaneous growth in vitro proliferation. Several cytokines including granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1), and tumor necrosis factor alpha (TNFa) have been implicated in supporting the growth of leukemic monocyte-macrophage colonies either by autocrine or paracrine pathways. In seven untreated JCML patients, we investigated the role of IL-1 in the spontaneous growth of these cells by specifically blocking IL-1 receptors. The IL-1 receptor antagonist (IL-1Ra) was added to the clonogenic assays, and in each case significant (mean = 63%, range = 35% to 82%) inhibition of spontaneous proliferation was observed. Uncultured circulating cells from PB or BM of four out of five patients expressed IL-1α-specific mRNA and secreted the protein into the culture supernatants. Moreover, by means of reverse transcriptase-polymerase chain reaction (RT-PCR), we demonstrated that most of the spontaneously growing leukemic colony-forming unit cells (CFU-C) obtained from BM cells of two patients were positive for the presence of the IL-1β-specific mRNA. Despite the presence of a measurable amount of GM-CSF in JCML cell culture supernatants, GM-CSF-specific mRNA in CFU-C cells of four cases was not detected by RT-PCR. These data further support a central role for IL-1β in the pathogenesis of JCML and suggest that the use of IL-1Ra could represent a novel therapeutic strategy against this disorder.

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Juvenile Chronic myelogenous leukemia (JCML) is a rare hematopoietic malignancy of early childhood distinct from the adult type of chronic myelogenous leukemia (CML). Characteristic of JCML are the absence of the Philadelphia chromosome (Ph1), elevated levels of fetal hemoglobin, hepatosplenomegaly, thrombocytopenia, and prominent monocytosis. In JCML patients, bone marrow (BM) progenitors show a unique ability to proliferate "spontaneously" in the absence of exogenous stimuli. The colonies derived from these patients give rise to a predominance of monocyte/macrophages over the granulocytic aggregates. Interleukin-1 (IL-1), tumor necrosis factor alpha (TNFα), and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been reported to be involved in autocrine or paracrine pathways of growth stimulation in acute myelogenous leukemias (AMLs) and CMLs including JCML. Bagby et al. reported that monocytes from JCML produce high levels of IL-1, which in turn stimulate the release of other CSFs by normal accessory hematopoietic cells. However, which of these cytokines is the primary regulator of the JCML cell proliferation remains unclear; moreover, no definitive evidence has been provided on the cell source of these growth factor molecules. A naturally occurring IL-1 inhibitor has been purified, cloned, and renamed IL-1 receptor antagonist (IL-1Ra). This molecule has been shown to inhibit the in vitro growth of leukemic cells isolated from both AML and CML during the accelerated phase of the disease. Based on these findings, we investigated gene and protein expression of IL-1β and GM-CSF in cells and clonogenic progenitors in these patients and the effect of IL-1 blockade on spontaneous growth using IL-1Ra.

MATERIALS AND METHODS

Patients. Between January 1986 and December 1992, the eight patients in this study were referred to our clinic. Table 1 summarizes the main clinical and laboratory data that fit into the classic description of JCML. These patients had varying degrees of hepatosplenomegaly, skin manifestations, and hemorrhagic signs. Most had leukocytosis, monocytosis, anemia, and a high level of fetal hemoglobin. BM aspirates showed normal cellularity with myeloid hypoplasia when BM smears were stained with May-Grünwald Giemsa. Cytogenetic analysis of BM cells revealed an apparently normal karyotype. For control studies, BM was obtained from five pediatric patients with classic Ph1+ CML and 10 normal children undergoing marrow harvesting for allogeneic BM transplantation. Approval was obtained from the Institutional Review Board for these studies. Informed consent was obtained according to the Declaration of Helsinki.

Cell preparations. Peripheral blood (PB) or BM cells were isolated on Ficoll-Hypaque (Pharmacia, Piscataway, NJ) density gradients and used for cell cultures and molecular studies. In selected experiments, PB or BM mononuclear adherent cells were removed by overnight incubation in plastic flasks (Falcon, Becton Dickinson, Plymouth, UK) in Iscove's modified Dulbecco's medium (IMDM Gibco, Paisley, Scotland, UK) with 10% fetal calf serum at 37°C to achieve a satisfactory depletion of adherent cells. Nonadherent cells were removed and contained less than 5% of monocytes as assessed by detecting the presence of the CD14 antigen using the Mo2 antibody (kindly provided by Dr R.F. Todd, University of Michigan, Ann Arbor, MI) by flow cytometry. The light-density cell fractions and depleted cell populations were then plated in clonogenic assays.

Clonogenic assays. BM and PB cells at a density of 103/mL and

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5 × 10^5/mL, respectively, were plated in IMDM supplemented with 20% fetal calf serum, ±10% 5637 conditioned medium, and 0.33% final concentration of Agar Bacto (Difco Laboratories, Detroit, MI) as previously described.9 The conditioned medium from the 5637 tumor cell line was used as a source of CSFs at a final concentration of 10%. All samples were cultured in the presence and absence of CSFs. The culture mixture was plated in a volume of 1 mL in 35-mm Petri dishes in triplicate. After a 14-day incubation at 37°C in a fully humidified atmosphere of 5% CO2 in air, colony-forming unit cells (CFU-C) were scored under an inverted microscope. Aggregates of more than 50 cells were evaluated as colonies.

To test the ability of the IL-1Ra to inhibit the clonogenic growth of JCML cells, recombinant IL-1Ra (kindly provided by Dr Daniel Tracey, Upjohn, Kalamazoo, MI) was added to the plates at concentrations ranging from 100 ng/mL to 1 µg/mL in the absence of 5637 conditioned medium. The specificity of the inhibitory effect of IL-1Ra and the lack of toxic contaminants in the preparation used was confirmed by clonogenic assay performed with normal BM stimulated with 5637 conditioned medium. To characterize the aggregates, cytocentrifuged preparations of individual colonies plugged from the plate were stained with May-Grünwald Giemsa for morphologic evaluation. Nonspecific α-naphthyl acetate and chloroacetate esterase staining and immunocytochemical analysis were used to identify the nature of colony-forming cells (Sigma Italia, Milano, Italy). The expression of surface antigens was assessed by the alkaline phosphatase anti-alkaline phosphatase (APAAP) technique, as previously described.10 A neutralizing monoclonal anti-human GM-CSF (clone 3092)11 was provided by Dr J. Griffin (Dana Farber Cancer Institute, Boston, MA). cDNA probes were labeled with 32P-deoxycytidine triphosphate by the method of Feinberg and Vogelstein.12 In selected experiments, total mRNA was directly isolated from JCML colonies after 14 days of culture, using the acid guanidium thiocyanate-phenol-chloroform method as previously described.8 Briefly, 200 µL guanidium buffer and 4 µg MS2 phage RNA (Boehringer, Mannheim, Germany) as a carrier were added to individual colonies following removal from agar. RNA was then extracted once by mixing with 200 µL phenol-40 µL chloroform-isooamyl alcohol. After

### Table 1. Clinical Profile of JCML Patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at diagnosis (mo)</th>
<th>Sex</th>
<th>Blood counts</th>
<th>Colony growth</th>
<th>Karyotype</th>
<th>Treatment status at time of cell culture studies</th>
<th>Survival (mo)</th>
<th>BM Cellularity*</th>
<th>BM Colony growth</th>
<th>BM Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>M</td>
<td>Hemoglobin (g/dL)</td>
<td>CFU-M</td>
<td>46, XY</td>
<td>Relapse</td>
<td>16</td>
<td>&gt;1</td>
<td>CFU-M</td>
<td>46, XY</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>M</td>
<td>WBC (×10^9/L)</td>
<td>CFU-M</td>
<td>46, XY</td>
<td>Relapse</td>
<td>2</td>
<td>&gt;1</td>
<td>CFU-M</td>
<td>46, XY</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>M</td>
<td>Blasts (%)</td>
<td>CFU-M</td>
<td>46, XY</td>
<td>Diagnosis</td>
<td>3</td>
<td>4</td>
<td>CFU-M</td>
<td>46, XY</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>M</td>
<td>Monocytess (%)</td>
<td>CFU-M</td>
<td>46, XY</td>
<td>Diagnosis</td>
<td>2</td>
<td>5</td>
<td>CFU-M</td>
<td>46, XY</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>M</td>
<td>Platelets (×10^9/L)</td>
<td>CFU-M</td>
<td>46, XY</td>
<td>Diagnosis</td>
<td>3</td>
<td>&gt;1</td>
<td>CFU-M</td>
<td>46, XY</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>F</td>
<td></td>
<td>CFU-M</td>
<td>46, XY</td>
<td>Diagnosis</td>
<td>5</td>
<td>5:1</td>
<td>CFU-M</td>
<td>46, XY</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>M</td>
<td></td>
<td>CFU-M</td>
<td>46, XY</td>
<td>Diagnosis</td>
<td>6</td>
<td>6:1</td>
<td>CFU-M</td>
<td>46, XY</td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>M</td>
<td></td>
<td>CFU-M</td>
<td>46, XY</td>
<td>Diagnosis</td>
<td>7</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: WBC, white blood cells; LAP, leukocyte alkaline phosphatase; BMT, bone marrow transplant; ND, not determined.

* Myeloid/erythroid ratio.

† Normal values, 11 to 94.

### Table 2. PB and BM CFU-C Growth in JCML Patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Time</th>
<th>Source</th>
<th>With CSA</th>
<th>Without CSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diagnosis</td>
<td>PBMC</td>
<td>20 ± 1</td>
<td>35 ± 9</td>
</tr>
<tr>
<td>2</td>
<td>Diagnosis</td>
<td>BM</td>
<td>7 ± 1</td>
<td>6 ± 3</td>
</tr>
<tr>
<td>3</td>
<td>Diagnosis</td>
<td>BM</td>
<td>148 ± 1</td>
<td>114 ± 5</td>
</tr>
<tr>
<td>4</td>
<td>Diagnosis</td>
<td>BM</td>
<td>10 ± 0</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>5</td>
<td>Diagnosis</td>
<td>BM</td>
<td>21 ± 1</td>
<td>40 ± 3</td>
</tr>
<tr>
<td>6</td>
<td>Diagnosis</td>
<td>BM</td>
<td>12 ± 1</td>
<td>20 ± 2</td>
</tr>
<tr>
<td>7</td>
<td>Diagnosis</td>
<td>BM</td>
<td>181 ± 1</td>
<td>192 ± 14</td>
</tr>
<tr>
<td>8</td>
<td>Diagnosis</td>
<td>BM</td>
<td>50 ± 17</td>
<td>664 ± 47</td>
</tr>
</tbody>
</table>

Ph1 + CML (5 cases) | Diagnosis | BM | 91 ± 3 | 6 ± 1 |

Data are presented as the mean of triplicate determinations.

Abbreviations: BM, bone marrow mononuclear cells; Ph1 + CML, Philadelphia-positive CML; nBM, bone marrow from hematologically normal patients; CSA, colony-stimulating activity.
centrifugation at 17,000 g for 20 minutes at 4°C, supernatant was precipitated with 2 vol 100% ethanol and finally resuspended in 20 μL of buffer for cDNA synthesis. In vitro reverse transcription of RNA to cDNA was performed in a 20-μL volume for 15 minutes at 42°C containing 2.5 U cloned Moloney murine leukemia virus reverse transcriptase and oligo deoxythymidylylithione as primers, using a commercial kit (GeneAmp RNA PCR kit, Perkin Elmer-Cetus, Norwalk, CT) according to manufacturer's conditions. A volume of 5 μL was then diluted in 100 μL final volume of buffer mixture containing 50 mmol/L KCl, 10 mmol/L Tris hydrochloride (pH 8.3 at 25°C), 2 mmol/L MgCl₂, 200 μmol/L deoxycytidine triphosphate, deoxyguanosine triphosphate, deoxyadenosine triphosphate, and deoxyribosylthymine triphosphate, 30 pmol of each primer, and 2.5 U Thermus Aquaticus DNA polymerase. The reaction was performed in a Thermal Cycler (Perkin Elmer-Cetus, Norwalk, CT) for 45 cycles; after the first 30 cycles, one fifth of the reaction mixture was removed and substituted with fresh reagents for the successive 15 cycles. The PCR temperatures used for each cycle were as follows: 95°C for 5 minutes as the denaturation step; then 95°C, 60°C, and 72°C for 1 minute each; and finally 10 minutes at 72°C. The primers used for IL-1β, included in a commercial kit (Perkin Elmer-Cetus), were 5'AAACAGATGAAGTGCTCCTTCCAGG-3' and 5'TGGAGAAACACCACTTGTTGCTCCA-3'. The primers used for GM-CSF were 5'-CTGCACCCGCGCTCG-3' corresponding to the 442 through 426 nucleotide residues and 5'-CACTCCTGGACTGGCTC-3' corresponding to residues 58 to 74 of the published GM-CSF sequence. Ten microliters of PCR mixture was run on a 1.8% NuSieve agarose gel (FMC BioProducts, Rockland, ME) stained with ethidium bromide and visualized under a UV lamp. In selected experiments, 10 μL PCR products fractionated by electrophoresis through a 1.8% agarose gel was transferred to nylon membranes (GeneScreen Plus, New England Nuclear, Boston, MA). Prehybridization, hybridization, and washings were performed according to manufacturer's instructions as previously reported. Measurement of cytokine production. IL-1β and GM-CSF levels were measured by specific, non-cross-reacting radioimmunoassays (RIAs). Each RIA has been validated using the cytokines in their respective biologic assay.

RESULTS

Spontaneous JCML cell proliferation in vitro. As shown in Table 2, when either PB or BM cells from JCML patients were cultured in the CFU-C assay, a significant number of colonies were observed in all cases in the absence of any deliberate source of colony-stimulating activity. By comparison, no significant growth of CFU-C was observed under the same conditions when normal or Ph+ CML BM cells were plated. Moreover, neither the total number nor the cell type of the colonies changed significantly when JCML cells were cultured in the presence of colony-stimulating factors. After careful depletion of adherent cells in selected experiments, a complete abrogation of the spontaneous colony growth was observed (cases no. 3, 4, 6, and 7; data not shown).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Time</th>
<th>Source</th>
<th>Medium</th>
<th>+IL-1Ra*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diagnosis</td>
<td>PBMC</td>
<td>35 ± 5</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>2</td>
<td>Diagnosis</td>
<td>PBMC</td>
<td>16 ± 3</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>3</td>
<td>Diagnosis</td>
<td>BM</td>
<td>114 ± 5</td>
<td>55 ± 1</td>
</tr>
<tr>
<td>4</td>
<td>Diagnosis</td>
<td>BM</td>
<td>12 ± 2</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>5</td>
<td>Relapse</td>
<td>BM</td>
<td>40 ± 3</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>6</td>
<td>Diagnosis</td>
<td>BM</td>
<td>20 ± 2</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>7</td>
<td>Diagnosis</td>
<td>BM</td>
<td>75 ± 1</td>
<td>40 ± 2</td>
</tr>
<tr>
<td>8</td>
<td>Diagnosis</td>
<td>BM</td>
<td>664 ± 47</td>
<td>156 ± 14</td>
</tr>
</tbody>
</table>

Data are presented as the mean of triplicate determinations.

Abbreviation: BM, bone marrow mononuclear cells.

* IL-1Ra at 100 ng/mL.
SUPPRESSION OF JCML CELL GROWTH BY IL-1RA

Pt. No 1 2 3 4 5

IL-1β —— A

Pt. No 1 2 3 4 5

IL-1ra —— B

Fig 2. Expression of IL-1β and IL-1Ra genes in JCML cells. Total cellular RNA was purified from uncultured PB cells of the indicated JCML patients, blotted, and hybridized to IL-1β- and IL-1Ra-specific probes.

shown). The monocyte feature of JCML cells, which were growing in the absence of colony-stimulating activity, CFU-M, as indicated in Table 1, was confirmed by the positive nonspecific esterase staining of a single JCML CFU-C aggregate (as shown in Fig 1B) and by the expression of CD14 antigen on a colony as assessed by immunochemistry (Fig 1D).

IL-1Ra inhibits spontaneous JCML cell proliferation in vitro. To block IL-1, we considered IL-1Ra based on our previous findings on the reduction in the spontaneous proliferation of AML cells.7 As shown in Table 3, when IL-1Ra was added to each clonogenic assay, we observed a significant inhibition of spontaneous JCML cell proliferation in each case (ranging from 35% to 82%). Increasing the concentration of IL-1Ra by 1 μg/mL did not result in a further abrogation of the spontaneous growth.

Cytokine gene expression in JCML cells. In light of the central role of IL-1β in supporting JCML cells, we investigated whether JCML cells expressed the IL-1β gene. As shown in Fig 2A, Northern analysis revealed IL-1β-specific mRNA in most cases (four of five). It is noteworthy that IL-1β gene expression was readily observed in RNAs purified from uncultured PB. Due to the comparable kinetics of IL-1β and IL-1Ra gene expression in normal human blood monocytes,19 we investigated the presence of IL-1Ra-specific mRNA. As indicated in the representative Northern analysis shown in Fig 2B, IL-1Ra mRNA was detected in the same cases that were positive for IL-1β gene expression. To investigate whether clonogenic cells were indeed the cellular source of IL-1β mRNA, PCR analysis of IL-1β gene expression was performed in selected cases. Figure 3 shows a representative experiment of PCR analysis for IL-1β gene expression conducted on six single BM colonies of patient no. 4. Superimposable results were obtained when the same experiment was performed on 12 BM colonies of patient no. 2 that were found to be consistently positive for IL-1β message. By comparison, a similar pattern of IL-1β gene expression was observed in CFU-C obtained from BM cells of normal individuals but in the presence of colony-stimulating factors (data not shown).

Because GM-CSF has also been reported to be involved in the regulation of JCML colony growth,20-21 we investigated GM-CSF gene expression in PB or BM JCML cells. Specific GM-CSF mRNA was not detected by Northern blot experiments when the same mRNA preparations, found to be positive for IL-1β or IL-1Ra gene expression, were hybridized with a GM-CSF cDNA probe (data not shown). To increase our capacity to detect GM-CSF-specific transcripts, PCR analysis was performed on total cellular RNA purified from PB and BM mononuclear cells of patients no. 1, 2, 4, and 7 (Fig 4). Since the GM-CSF transcript was found in BM and PB cells of patient no. 4 only, we speculated that this could be due to contamination of a minor proportion of cells. Interestingly, when PCR analysis for GM-CSF expression was performed on six colonies from patients no. 1 and 4 and 12 from patient no. 2, no GM-CSF-specific mRNA was detected (data not shown). Despite the absence of GM-CSF mRNA in single JCML colony preparations, GM-CSF was detected in JCML cell culture supernatant derived from 24- and 48-hour liquid culture specimens from case no. 1 (>2.50 pg/mL). Moreover, anti-human GM-CSF induced a significant suppression (40%) of JCML colony growth in case no. 8 (data not shown).

DISCUSSION

The in vitro "autonomous" proliferation of BM or PB cells with monocyte-macrophage features has emerged as one of the peculiar biological features of JCML.3 Similar to the studies of Estrov et al5 and Freedman et al,2 we confirmed the proliferation of monocyte-macrophage clonogenic cells of untreated JCML patients in the absence of any deliberate source of growth factors and that the depletion of adherent cells abrogated spontaneous colony formation, further supporting the central role of monocyte-macrophage cells in the mechanism of the disease.
Several cytokines including GM-CSF, TNFα, and IL-1 have been shown to support the abnormal growth of malignant cells of monocyte-macrophage lineage by either autocrine or paracrine pathways. In the present study, we found that IL-1Ra inhibited spontaneous JCML cell proliferation and that in most cases the inhibition was profound. Similar observations were recently reported by Rambaldi et al. and Estrov et al., who described the suppression of acute myeloblastic leukemia and CML colony growth by IL-1Ra. Because of the role of IL-1 in the multiple autocrine circuits operating within a single malignant myeloid clone, IL-1Ra likely exerts its suppressive action on colony growth by blocking the interaction between the IL-1 endogenously produced and the leukemic cells. Bagby et al. first reported that the abnormal proliferative activity of JCML cells was dependent in part on the abnormal production of IL-1, which in turn stimulated the production of colony-stimulating activity by accessory cells. In this context, it is noteworthy that the findings that either freshly obtained circulating cells or CFU-C from either PB or BM cells of JCML patients expressed IL-1β-specific mRNA and secreted the protein in the short-term culture (data not shown). It has also been shown that IL-1α could act directly to support CML colony growth, but not to the same magnitude as TNFα or GM-CSF.

Alternatively, IL-1 could exert its effect by inducing the secretion of GM-CSF and/or other growth factors, as shown for a variety of target cells. Several studies have implicated GM-CSF as the primary endogenous regulator of JCML cell proliferation. We were not able to detect GM-CSF transcripts in mRNA preparations from single JCML colonies, but, as previously reported, GM-CSF was de-
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tected in the culture supernatants from either PB or BM JCML cells. Since anti-human GM-CSF consistently inhibited cell proliferation, it is likely that the autocrine secretion of TNFα and/or IL-1β by the proliferating population of malignant monocyte-macrophages stimulates the production of GM-CSF by accessory cells.4

Under the same experimental conditions where IL-1β mRNA was detected in PB or BM JCML cells, we observed significant IL-1Ra gene expression. This finding is not surprising, since comparable kinetics in IL-1β and IL-1Ra induction are observed in normal PB mononuclear cells and GM-CSF is a potent stimulus for the production of IL-1Ra by normal human monocytes.5

In conclusion, our data implicate a central role for IL-1β in JCML and suggest that blocking IL-1 with molecules such as IL-1Ra could provide a novel therapeutic strategy against this disorder.

REFERENCES


Suppression of juvenile chronic myelogenous leukemia colony growth by interleukin-1 receptor antagonist [see comments]

R Schiro, D Longoni, V Rossi, O Maglia, A Doni, M Arsura, G Carrara, G Masera, E Vannier and CA Dinarello