Phenylarsine Oxide Blocks Interleukin-1β–Induced Activation of the Nuclear Transcription Factor NF-κB, Inhibits Proliferation, and Induces Apoptosis of Acute Myelogenous Leukemia Cells

By Zeev Estrov, Sunil K. Manna, David Harris, Quin Van, Elihu H. Estey, Hagop M. Kantarjian, Moshe Talpaz, and Bharat B. Aggarwal

Arsenic compounds have recently been shown to induce high rates of complete remission in patients with acute promyelocytic leukemia (APL). One of these compounds, As$_2$O$_3$, induces apoptosis in APL cells via a mechanism independent of the retinoic acid pathway. To test the hypothesis that arsenic compounds may be effective against other forms of acute myelogenous leukemia (AML), we studied the membrane-permeable arsenic compound phenylarsine oxide (PAO). Because interleukin-1β (IL-1β) plays a key role in AML cell proliferation, we first tested the effect of PAO on OCI/M2 and OCI/AML3 AML cell lines, both of which produce IL-1β and proliferate in response to it. We found that PAO inhibited the proliferation of both OCI/M2 and OCI/AML3 cells in a dose-dependent fashion (0.01 to 0.1 μmol/L) and that IL-1β partially reversed this inhibitory effect. We then measured IL-1β levels in these cells by using an enzyme-linked immunoabsorbent assay and Western immunoblotting and found that PAO almost completely abolished the production of IL-1β in these AML cells, whereas it did not affect the production of IL-1 receptor antagonist. Because PAO inhibits activation of the transcription factor NF-κB and induces apoptotic cell death in AML cells. We found that PAO induced apoptosis in OCI/M2 cells through activation of the cysteine protease caspase 3 and subsequent cleavage of its substrate, the DNA repair enzyme poly (ADP-ribose) polymerase. The PAO-induced apoptosis was caspase dependent, because it was completely blocked by the caspase inhibitor Z-DEVD-FMK. Finally, we tested the effect of PAO on fresh AML marrow cells from 7 patients with newly diagnosed AML and found that PAO suppressed AML colony-forming cell proliferation in a dose-dependent fashion. Taken together, our data showing that PAO is an effective in vitro inhibitor of AML cells suggest that this compound may have a role in future therapies for AML.

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MATERIALS AND METHODS

Cell lines. The AML cell lines OCI/AML3 and OCI/M2 were kindly provided by M.D. Minden (Ontario Cancer Institute, Toronto, Ontario, Canada). OCI/AML3 was established from an AML patient and OCI/M2 from a patient with erythroleukemia. Both cell lines proliferate in the presence of culture medium and fetal calf serum (FCS) without exogenous growth factors. The leukemia cell line HL60 and K562 were obtained from the American Type Culture Collection (ATCC; Rockville, MD). All cells were maintained in RPMI-1640 culture medium (GIBCO, Grand Island, NY) supplemented with 10% FCS (Flow Laboratories, McLean, VA).
Subjects. BM aspirates were obtained from 7 AML patients with high marrow blast counts (see Table 1 for clinical data). All studies were performed with the patients’ informed consent and were approved by the Human Experimentation Committee of our institution.

Cell line clonogenic assay. Clonogenic assays were performed as previously described. Briefly, OCI/AML3, OCIM2, HL60, and K562 cells (2 to 4 × 10⁵ cells/mL) were cultured in 0.8% methylcellulose (Fluka Chemical Corp, Ronkonkoma, NY), 10% FCS, and RPMI-1640 medium in the presence of PAO (Aldrich, Milwaukee, WI), which was dissolved in dimethyl sulfoxide (DMSO) at a concentration of less than 0.1%, with or without 10 ng/mL recombinant human (rh) IL-1β (molecular weight 17,500; Boehringer Mannheim Biochemicals, Indianapolis, IN). The culture mixture was placed in 35-mm Petri dishes (Nunc Inc, Naperville, IL) in duplicate or triplicate and maintained at 37°C with 5% CO₂ in air in a humidified atmosphere. Colonies were counted after 7 days by using an inverted microscope. A colony was defined as a cluster of more than 40 cells.

Enzyme-linked immunosorbent assay (ELISA). ELISAs were performed with IL-1β and IL-1 receptor antagonist (IL-1RA) ELISA kits (Cistron Biotechnology [Pine Brook, NJ] and Amersham Life Science [Arlington Heights, IL], respectively) as previously described. Cell lysates and standard dilutions of either IL-1β or IL-1RA were added to test wells in duplicate and incubated for 2 hours at 37°C. The test wells were then washed 3 times with phosphate-buffered saline (PBS), incubated with rabbit IL-1β antisera for 2 hours, washed as previously described, and incubated for 30 minutes with goat antirabbit IgG conjugated to horseradish peroxidase. The test wells were vigorously washed, and a substrate (o-phenylenediamine dissolved in 3% hydrogen peroxide solution) and 4 N sulfuric acid were added. The color intensity was read within 15 minutes at a wavelength of 490 nm with a microplate reader (Titertek, Madison, WI) was used to perform TUNEL assays. 23 Briefly, 4% of apoptosis.

Table 1. Clinical Data on AML Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Cytogenetic Abnormality</th>
<th>FAB Category</th>
<th>Hb (g/dL)</th>
<th>WBC (&lt;10⁹/L)</th>
<th>Platelets (&lt;10⁹/L)</th>
<th>% Blasts in BM</th>
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<tr>
<td>1</td>
<td>44/F</td>
<td>Misc</td>
<td>M2</td>
<td>6.3</td>
<td>129</td>
<td>87</td>
<td>96</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>78/M</td>
<td>5 – 7</td>
<td>M2</td>
<td>10.3</td>
<td>14.5</td>
<td>26</td>
<td>74</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>67/F</td>
<td>Misc</td>
<td>M4</td>
<td>9.9</td>
<td>18.7</td>
<td>95</td>
<td>69</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>40/M</td>
<td>Dip, t(v)</td>
<td>M2</td>
<td>8.0</td>
<td>19.3</td>
<td>16</td>
<td>61</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>69/F</td>
<td>t(15;17)</td>
<td>M2</td>
<td>8.2</td>
<td>6.7</td>
<td>53</td>
<td>88</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>64/F</td>
<td>Misc</td>
<td>M1</td>
<td>11.0</td>
<td>146.9</td>
<td>16</td>
<td>92</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>45/F</td>
<td>5 – 7</td>
<td>M1</td>
<td>8.1</td>
<td>6.3</td>
<td>11</td>
<td>53</td>
<td>93</td>
</tr>
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</table>

Abbreviations: FAB, French-American-British; Hb, hemoglobin; WBC, white blood cells; Misc, miscellaneous; Dip, Diploid.
formaldehyde-treated cytospun cells were made permeable with 0.2% Triton-100 in PBS. After washing, slides were treated with equilibration buffer (supplied with kit) and then incubated with a TdT buffer (prepared according to the manufacturer’s instructions) for 60 minutes. The staining reaction was terminated by treating the slides with 2× SSC for 15 minutes. After washing, the slides were treated with an anti-fade solution and then mounted on slides with glass coverslips and rubber cement. The slides were analyzed using a fluorescence microscope.

**Western immunoblotting for detection of caspase 3 and PARP proteins.** Cell lysates (from 5×10^5 cells) were used as described above. The following antibodies were used to detect the relevant proteins: monoclonal mouse antihuman CPP32 (Transduction Laboratories, Lexington, KY) to detect uncleaved caspase 3, and mouse antihuman PARP (Upstate Biotechnology, Lake Placid, NY) to detect PARP. Normal mouse IgG and normal rabbit serum were used as a control. To confirm detection of uncleaved caspase 3, Jurkat cells (ATCC) were used; to confirm detection of cleaved caspase 3 and PARP, 3T3 cells (ATCC) and HeLa cell (ATCC) nuclear extracts were used, respectively. Bound antibody was detected according to the ECL protocol (Amersham Life Science) as described above.

**Adherent-cell fractionation.** Low-density BM mononuclear cells obtained by Ficoll-Hypaque (Pharmacia, Piscataway, NJ) fractionation were incubated in plastic tissue-culture dishes or flasks (Falcon Plastics; Becton Dickinson, Oxnard, CA) with 10% FCS in α-medium (GIBCO). The fractionation procedure was repeated until no cells adhered to the tissue-culture dishes. Nonadherent cells harvested in this way contained less than 3% monocytes, as confirmed by the following techniques: (1) microscopic differential counting of at least 100 cells prepared with Wright’s stain and (2) nonspecific (α-naphthyl butyrate) esterase staining and immunocytochemical analysis with CD14 monoclonal antibodies (Becton Dickinson) to identify monocyte-promonocyte cells, as previously described.24,25

**T-cell depletion.** T cells were depleted from the nonadherent fraction by negative immunomagnetic selection.26 In a modification of this technique, nonadherent BM cells were incubated with CD3 monoclonal antibodies (Becton Dickinson) at a concentration of 1 µg/10^6 cells in PBS with 0.25% FCS for 30 minutes at 4°C. The labeled cells were washed 3 times and then incubated with goat antimouse IgG-conjugated immunomagnetic beads (Advanced Magnetics, Cambridge, MA) at 4°C for 60 minutes in an end-over-end rotation at a 20:1 bead:cell ratio. Immunomagnetic bead-rosetted cells were removed with a magnetic particle concentrator (Advanced Magnetics), and unrosetted cells remaining in suspension were harvested by a Pasteur pipette. In some experiments, this procedure was repeated twice. The T-lymphocyte–depleted population contained less than 3% CD3 cells as assessed by an immunocytochemical technique performed on cytospun cells.24,25

**AML blast colony assay.** A previously described method was used to assay AML blast colony formation.27,28 Briefly, 1×10^5 nonadherent T-cell–depleted BM cells were plated in 0.8% methylcellulose in α-medium supplemented with 10% FCS and 50 ng/mL recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF; Immunex Corp, Seattle, WA). PAO was dissolved in DMSO and added at the initiation of the cultures at concentrations ranging from 0.01 to 0.1 µmol/L in the absence or presence of 10 U/mL of IL-1β. The cultures were incubated in 35-mm Petri dishes in duplicate or triplicate for 7 days at 37°C in a humidified atmosphere of 5% CO₂ in air. AML blast colonies were microscopically evaluated on day 7 of culture. A blast colony was defined as a cluster of 20 or more cells. Individual colonies were plucked, smeared on glass slides, and stained to confirm their leukemic cell composition. (That the AML blast colony assay identifies blasts rather than normal progenitors had been previously demonstrated by cytogenetic analysis of colonies obtained using this assay.)

**RESULTS**

**PAO inhibits leukemia cell line colony proliferation.** We began studying the effect of PAO on the proliferation of OCI/AML3 and the OCIM2 cell lines and found that PAO suppressed their colony-forming cell growth in a dose-dependent fashion at concentrations ranging from 0.01 to 0.1 µmol/L (Fig 1, upper panel). Although the OCI/AML3 cells were more sensitive to PAO than were OCIM2 cells, both cell
lines were much more sensitive to PAO than either HL60 or K562 cells. Indeed, the growth of OCI/AML3 and OCIM2 cells was almost completely abolished by PAO at concentrations of 0.05 and 0.1 µmol/L, respectively, whereas HL60 and K562 cells were only partially inhibited (27% and 61%, respectively) by 0.1 µmol/L (Fig 1, lower panel). The DMSO that was used to dissolve PAO had no effect on the proliferation of either cell line.

**IL-1β partially reverses the inhibitory effect of PAO.** Because OCI/AML3 and OCIM2 cells, unlike HL60 and K562 cells, proliferate in response to IL-1β, we also tested whether IL-1β could affect the inhibitory effect of PAO. We found that 10 ng/mL IL-1β added at the initiation of culture partially reversed PAO’s suppressive effect (Fig 2). This is in keeping with previous studies in which we found that (1) OCI/AML3 and OCIM2 cells produce large quantities of IL-1β, which maximally stimulates their proliferation in an autocrine fashion; (2) the addition of exogenous IL-1β could not significantly stimulate their further growth; and (3) IL-1β antibodies could suppress their growth. Our current results therefore suggested that PAO might suppress IL-1β production by OCI/AML3 and OCIM2 cells.

**PAO inhibits IL-1β protein production.** In light of the results given above and published data indicating that PAO inhibits NF-κB, a binding site known to be present in the IL-1β promoter, we hypothesized that PAO inhibits IL-1β. To test this idea, we first incubated the cells with PAO and measured IL-1β protein levels in lysates of OCI/AML3 and OCIM2 cells. Using ELISAs, we found that 24 hours of incubation with 0.1 µmol/L PAO significantly reduced the production of IL-1β but not of IL-1RA protein by both cell types (Fig 3). These results indicated that the effect of PAO on IL-1β production is specific and does not result from a general suppression of protein synthesis. Because the ELISA detects both the uncleaved and cleaved forms of IL-1β, we also used Western immunoblotting to measure active (cleaved) IL-1β in OCIM2 line, whose morphology and origin do not resemble those of APL, and...
found that PAO significantly suppressed the production of mature IL-1β (Fig 4).

PAO inhibits IL-1β–induced NF-κB activation. Because IL-1 is known to activate NF-κB, we sought to determine whether IL-1β activates NF-κB in OCIM2 cells. We did so by incubating the cells for 1 hour in the presence of increasing concentrations of IL-1β and then testing them for NF-κB activity by EMSA. As shown in Fig 5A, NF-κB activation increased with IL-1β dose, reaching a maximum at 10 ng/mL IL-1β. Next, we examined the effect of increasing concentrations of PAO on IL-1β–induced NF-κB activation. For this, OCIM2 cells were treated for 1 hour with 0.1, 0.3, and 1.0 µmol/L PAO and then for 1 more hour with the addition of 10 ng/mL IL-1β. As shown in Fig 5B, PAO abolished the IL-1β–induced NF-κB activation in a dose-dependent manner, with maximum inhibition occurring at a PAO concentration of 1.0 µmol/L (the minor activation of NF-κB induced by 1.0 µmol/L of PAO was not significant by a quantitative analysis, as found in our previous study).

The specificity of the NF-κB band in the EMSAs was demonstrated by its ability to compete with a cold oligo but not with an oligo containing a mutated NF-κB site. Thus, these results show that PAO blocked IL-1β–induced NF-κB activation.

PAO induces apoptosis in OCIM2 cells. Because a lack of NF-κB activation may abolish cellular proliferation and lead to apoptotic cell death and the arsenic compound AS2O3 can induce apoptosis in APL cells, we hypothesized that PAO might have a similar effect on OCIM2 cells. To test this idea, OCIM2 cells at the peak of their growth were washed and then incubated in PBS in the presence and absence of 0.1 µmol/L PAO for 4, 6, and 8 hours. Using the TUNEL assay, we found that PAO induced apoptosis in these AML cells and that longer exposure to this compound increased the number of cells undergoing apoptotic cell death (Fig 6).

PAO induces apoptosis by cleaving caspase 3. To determine the mechanism by which PAO induces apoptosis, OCIM2 cells were incubated in the absence and presence of 0.06, 0.08, 0.1, 0.4, 0.6, and 0.8 µmol/L of PAO for 4 hours and then harvested for Western immunoblot analysis as described above. As shown in Fig 7, PAO downregulated the expression of uncleaved PARP protein in a dose-dependent fashion. Because caspase activation seems to be an essential step in PARP cleavage and cellular apoptosis and because caspase 3 appears to be involved in apoptosis induced in leukemia cells, we measured the levels of uncleaved and cleaved caspase 3 in OCIM2 AML cells. As shown in Fig 8, we found that the incubation of OCIM2 cells with 0.08 and 0.1 µmol/L of PAO upregulated the levels of the biologically active (cleaved) caspase 3 and the inactivated (cleaved) form of the DNA-repair enzyme PARP, thereby activating the apoptotic cascade. To further investigate whether caspase activation is essential for PAO-induced apoptosis, we incubated OCIM2 cells with 0.1 µmol/L of PAO with and without 50 µmol/L of the caspase inhibitor Z-DEVD-FMK. Using the TUNEL assay, we
found that Z-DEVD-FMK completely blocked PAO-induced apoptosis (Fig 9).

PAO inhibits fresh AML blast colony-forming cell proliferation. We then studied the effect of PAO on the proliferation of fresh AML marrow blast colony-forming cells. For this, we used diagnostic BM cells from 7 AML patients whose clinical characteristics are depicted in Table 1. As shown in Fig 10, PAO inhibited AML blast colony-forming cell growth in a dose-dependent manner in all of the samples studied. Similar to its effect on AML cell lines, IL-1β, when added at the initiation of culture, partially reversed the inhibitory effect of PAO (Fig 11).

DISCUSSION

Throughout history, arsenic compounds have been useful therapeutic agents against many human ailments. The antileukemic properties of arsenic have been known since the mid 1800s. Arsenicals together with irradiation were the treatment of choice for chronic myelogenous leukemia until busulfan was

**Fig 6.** Induction of apoptosis by PAO. OCIM2 cells were incubated in the absence (A) and presence of PAO for 4 (B), 6 (C), and 8 (D) hours. Apoptotic cells appear yellow.

**Fig 7.** Induction of apoptosis by PAO. OCIM2 cells were incubated in the absence (A) and presence of PAO for 4 (B), 6 (C), and 8 (D) hours. Apoptotic cells appear yellow.

**Fig 9.** Effect of Z-DEVD-FMK on PAO-induced apoptosis. OCIM2 cells were incubated for 6 hours without any drug (A), with 0.1 μmol/L of PAO (B), with 50 μmol/L of Z-DEVD-FMK (C), and with both PAO and Z-DEVD-FMK (D). Apoptotic cells appear yellow.
introduced in 1953. However, in the late 20th century, research has concentrated on the toxic effects of arsenic compounds. Several investigators have shown a relationship between ingestion of or exposure to various arsenicals and the occurrence of lung, skin, bladder, and hepatocellular cancer, and numerous studies have demonstrated that arsenic compounds are environmental carcinogens. Yet, recent reports from China show that As$_2$O$_3$ and arsenic disulfide can induce complete remission of APL via pathways different from those used by retinoids. These studies have prompted other investigators to explore the effects of various arsenicals on APL and other leukemias.

The arsenical PAO is a membrane-permeable PTPase inhibitor that is active in hematopoietic cells. At high concentrations it causes nonspecific leakage in mitochondria. PAO also has been shown to inhibit early elevations in cytosolic calcium concentrations and to interfere with the insulin transduction pathway. Because PAO is also known to inhibit the activation of NF-$\kappa$B in hematopoietic cells, we therefore sought to investigate its effects on AML.

NF-$\kappa$B is a ubiquitous transcription factor and a major regulator of the immune system through its induction of expression of various inflammatory cytokines including IL-$\beta$. NF-$\kappa$B exists in the cytoplasm as a heterotrimeric complex with the inhibitor IκB (reviewed in Seibenlist et al). Within minutes of activation by inflammatory agents such as IL-$\beta$, IκB undergoes phosphorylation, ubiquitination, and proteolytic degradation, thus releasing the NF-$\kappa$B p50-p65 complex for translocation from the cytoplasm to the nucleus. Whereas the activation of NF-$\kappa$B induces cellular proliferation and protects cells from apoptotic cell death, its inhibition enhances spontaneous apoptosis or apoptosis induced by various stimuli such as irradiation or cytotoxic drugs.

Several growth factors regulate hematopoietic cell survival by interfering with apoptotic signals. One of these is the cytokine IL-$\beta$, a proinflammatory protein that has been implicated in early events in hematopoiesis. It induces the production of various cytokines and synergizes with several growth factors in stimulating hematopoietic progenitor multiplication. In addition, as we and others have found, IL-$\beta$ plays an important role in AML cell proliferation (reviewed in Estrov et al). Suppression of IL-1 production or inhibition of its interaction with the corresponding cellular receptors significantly inhibits AML progenitor cell growth. Furthermore, the activation of NF-$\kappa$B appears to be an important step in the molecular events leading to IL-$\beta$ production and, as a result, also appears to stimulate leukemia cell proliferation.

In this light, we assumed that an effective NF-$\kappa$B inhibitor such as PAO might either suppress the production of IL-$\beta$, inhibit the direct NF-$\kappa$B–mediated leukemia cell proliferation, or both. In a previous study we have already demonstrated that PAO can block the NF-$\kappa$B–dependent expression of various
adhesion molecules, thus suggesting that PAO inhibits the activity of NF-κB. Now, in our current study, we have found that PAO inhibits the proliferation of HL60 and K562 and, more significantly, of the IL-1-responsive OCI/AML3 and OCIM2 cells, that PAO suppressed the growth of the IL-1-responsive lines in a dose-dependent manner, and that IL-1β partially reverses this inhibitory effect. Together, these results suggest that at least part of the PAO-induced suppression observed in the present study was mediated through PAO’s inhibition of IL-1β production. Indeed, incubation of the OCI/AML3 and OCIM2 cell lines in the presence of PAO almost completely abolished the production of IL-1β but not IL-1RA protein. In addition, PAO significantly inhibited the IL-1β–induced NF-κB activity. Whereas IL-1β activated NF-κB in these cells, PAO suppressed it in a dose-dependent fashion. Thus, PAO inhibited both IL-1β production and the IL-1β–mediated activation of NF-κB, resulting in an additional reduction in the production of IL-1β.

Because NF-κB activation suppresses the signals for cell death and inhibition of the effect of NF-κB may result in apoptotic cell death,34,35 we tested the effect of PAO on the induction of apoptosis. We found that treatment of leukemia cells with PAO induced apoptotic cell death. Our results agree with those of Jimi et al.,71 who recently found that inhibition of NF-κB by oligodeoxynucleotides to p65 and p50 abolished the IL-1–induced survival of osteoclasts.

Because most cell types require activation of a specific proteolytic cascade if apoptosis is to occur, we also wondered whether PAO might help activate that cascade in AML cells. In particular, we chose to study the effect of PAO on caspase 3. Caspase 3 is a key executioner of apoptosis whose activation downstream in the apoptotic cascade is essential for leukemia cell apoptosis.33,42,43 Moreover, the activation of caspase 3 results in the cleavage of cellular substrates critical for cell survival, such as PARP and laminas, which, in turn, precipitates the morphological changes characteristic of apoptosis (reviewed in Cohen). This approach of ours found support in the work of Zhang et al.,73 who had already shown that arsenic trioxide downregulates the expression of bel-2, an antiapoptotic protein known to inhibit the activation of caspase 3. As hoped, we found that PAO activated caspase 3 and consequently cleaved PARP. Interestingly, Barkett et al.74 have recently reported that caspase 3 cleaves human IκB-α in vitro at a conserved Asp-Ser sequence, thus creating a dominant inhibitor that prevents the activation of NF-κB and thereby adding another death signal.

Similar to its effect on AML cell lines and comparable to the effect of other IL-1 inhibitors, PAO suppressed AML progenitor proliferation and had its inhibitory effect partially reversed by IL-1β. These results indicate that the inhibition of IL-1β production is part of PAO’s inhibitory mechanism in AML cells.

Taken together, our data suggest that PAO, either through inhibition of NF-κB, suppression of IL-1β production, or both, may eliminate leukemia cells and so prove to be an effective agent in the treatment of AML.

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