Use of a Lethally Irradiated Major Histocompatibility Complex Nonrestricted Cytotoxic T-Cell Line for Effective Purging of Marrows Containing Lysis-Sensitive or -Resistant Leukemic Targets

By Alessandra Cesano, Giuliana Pierson, Sophie Visonneau, Anna Rita Migliaccio, and Daniela Santoli

Improved marrow purging protocols are needed in autologous bone marrow transplantation (BMT) to achieve complete eradication of minimal residual disease. This study investigates the potential of a human major histocompatibility complex (MHC) nonrestricted killer T-cell line (TALL-104) as a new marrow purging agent in a clinical setting. TALL-104 cells can be irradiated without losing cytotoxic activity against tumor targets in vitro. In vivo, the irradiated killers can be adoptively transferred into immunodeficient and immunocompetent leukemia-bearing mice, and reverse their disease even in advanced stages. The present study shows that γ-irradiated TALL-104 cells, cultured for 18 hours with marrows from healthy donors, do not impair the viability and long-term growth of committed and pluripotent hematopoietic progenitors. However, as determined by polymerase chain reaction (PCR) and colony assays, TALL-104 cells could completely purge marrows containing up to 50% lysis-susceptible myelomonocytic leukemia cells (U937). When marrows were admixed with a pre-B leukemia cell line (ALL-1), which is fairly resistant to TALL-104 cell lysis in long-term Cr-release assays but can be totally growth inhibited by TALL-104 cells in proliferation assays, residual ALL-1 cells were detectable by PCR after TALL-104 purging. However, importantly, these PCR marrow were devoid of tumorigenic activity when transplanted into the human hematopoietic microenvironment of human severe combined immunodeficient (SCID) chimeras. These data indicate the strong potential of the TALL-104 cell line in future marrow purging strategies against lysis-susceptible and -resistant leukemias. © 1996 by The American Society of Hematology.

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393
used to cleanse remission marrows and might even be used in consolidative therapy after autologous BMT.

This report investigates at the cellular and molecular levels the marrow purging efficacy of lethally irradiated TALL-104 cells against susceptible and resistant leukemic targets, and the effects of this approach on the growth of normal BM precursors, which are necessary for the patient’s hematopoietic reconstitution.

MATERIALS AND METHODS

Cell lines. The TALL-104 cell line was maintained at 37°C in 10% CO2 in Iscove’s modified Dulbecco’s medium (IMDM) supplemented with 10% fetal bovine serum (FBS) (complete medium) and 100 U/mL of recombinant human (rh) IL-2 (a gift from Dr M. Gately, Hoffman LaRoche, Nutley, NJ). The human tumor cell lines U937 (myelomonocytic leukemia), Raji (B-cell lymphoma), ALL-1 (pre-B-ALL), U-87 MG (glioblastoma), A549 (lung carcinoma), CHP-100 (neuroblastoma), and WM1985 (melanoma) were cultured in complete medium. All cell lines were free of mycoplasma contamination on repeated testing. Human melanocytes were obtained from Dr M. Herlyn (The Wistar Institute) immediately after their separation and the effects of this approach on the growth of normal hematopoietic reconstitution.

Tagging of U937 cells with a neomycin-resistance (neo-R) gene. The N2A double copy retroviral vector, containing the neo-R gene, was expressed as 30% LU/10^6 effectors, as described.23

Normal and leukemic BM cells. BM aspirated from the iliac crest of healthy donors was centrifuged on a Ficoll-Hypaque gradient to use a nonproducer U937 clone. G-418 (1 mg/mL) was added to the marrow purging efficacy of lethally irradiated TALL-104 cell lysis, measured in a 4-hour Cr release assay, was identical to that of the parental U937 cell line.

Normal BM cells. All cell lines were free of mycoplasma contamination on repeated testing. Human melanocytes were obtained from Dr M. Herlyn (The Wistar Institute) immediately after their separation and the effects of this approach on the growth of normal hematopoietic reconstitution.

Hematopoietic progenitor cell assay. To assess the growth of hematopoietic progenitors, 1 × 10^6 total BM mononuclear cells or 1 × 10^6 CD34-enriched cord blood samples were cultured in Iscove’s methylcellulose medium containing erythropoietin- and phytohemagglutinin-stimulated leukocyte conditioned medium (CM) (Method HCC-4432; Stem Cell Technologies, Vancouver, BC, Canada) using standard procedures.38 Briefly, cultures were plated in 35-mm culture dishes (Nunc Inc, Naperville, IL) in duplicates and incubated at 37°C for 7 days. Hematopoietic colony parameters were determined on day 14 under an inverted microscope to identify and count BFU-E, more mature erythroid progenitor colonies (CFU-E), CFU-GM, and CFU-GEMM. The latter are identified by the presence of erythroid and myeloid elements in the same colony; BFU-E are red, hemoglobinized colonies composed of two or more large clusters; CFU-E contain red blood cells (RBCs) in a single cluster; CFU-GM colonies are composed of non-RBCs and have a translucent appearance. Colonies are defined as aggregates of 50 cells or more.

Cytokine assays. The presence of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) in the CM of TALL-104 cells cultured
A CYTOTOXIC T-CELL LINE FOR MARROW PURGING

for 18 hours either alone or with BM/tumor cell mixtures was tested by radioimmunooassays, as described, using monoclonal antibodies supplied by Dr. G. Trinchieri (The Wistar Institute). The presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) in the same CM was quantitated by ELISA using a commercially available kit (R&D, Minneapolis, MN). The sensitivity of the ELISA test was 16 pg/mL. In some experiments, TALL-104 cells were pretreated for 2 hours with Actinomycin D (Calbiochem, Novabiochem Corp, San Diego, CA; 10 μg/mL) and Puromycin (Sigma, St Louis; 50 μg/mL) to block protein synthesis, and washed three times in saline before incubation for 18 hours with untreated BM cells. The same Actinomycin/Puromycin treatment was applied to BM cells before incubation with untreated TALL-104 cells. CM from all of these cultures were then collected and tested for the presence of cytokines.

RNA blot analysis. Total RNA was extracted from the above Actinomycin/Puromycin-treated TALL-104/BM cultures using the RNAzol method (CinnalSiotech Laboratories International Corp, Friendswood, TX). RNA samples were fractionated in a 1% agarose formaldehyde gel, transferred to nylon membrane filters (Zetabind AMF; Cuno, Meridian, CT), and covalently bound to the membranes by UV irradiation. Filter-bound RNA was hybridized at 42°C for 16 hours with 106 cpm/mL of neo-R gene-specific probes (whole plasmid preparations, provided by Dr G. Trinchieri and the Genetics Institute) specific for GM-CSF, IFN-γ, and TNF-α were used for RNA analysis.

Engraftment of human tissue in immunodeficient mice. Human fetal bone tissue was obtained with informed consent from the International Institute for the Advancement of Medicine (Exton, PA) in compliance with regulations issued by each state and the Federal government. The tissues, derived from curettage operations, were individually placed in sterile 50-μL tubes containing complete medium and antibiotics, shipped on wet ice, received within 16 to 20 hours, and transplanted immediately into SCID mice. The construction of SCID-human chimeras with fetal long bone implants was obtained by implanting subcutaneously small fragments (approximately 5 × 5 × 10 mm) from femurus and tibias of 19- to 23-gestational-week-old fetuses, as described by Namikawa et al. This system allows for the closed expansion of leukemic cells within the human bone grafts precluding dissemination in the peripheral blood (PB), marrow, and other murine tissues.

Detection of residual leukemia. BM samples were mixed with various concentrations of neo-R U937 cells or ALL-1 cells, as indicated. IL-2/IL-12-stimulated, γ-irradiated TALL-104 cells were added for 18 hours. The cell mixture was washed and treated with DNase I (10 μg/mL) to rid cell-free DNA. Cellular DNA was extracted by lysing the cells in 100 μL lysis buffer (50 mmol/L KCl, 10 mmol/L Tris-HCl, pH 8.3, 2.5 mmol/L MgCl2, 0.45% NP-40, and 0.45% Tween 20) with an added 0.6 μL proteinase K (10 mg/mL). Lysates were left for 1 hour at 55°C, and 10 more minutes at 95°C. DNA (1 μg/100 μL) was subjected to polymerase chain reaction (PCR) amplification using either neo-R gene-specific primers, to detect U937 cells, or VJ primers specific to the CD3 region of ALL-1 cells. The sequences amplified by these primers are of 501 bp, and 189 base pairs, respectively. Oligonucleotide probes recognizing 20 nucleotides in the middle of the amplified sequences were used to show the specificity of the PCR products.

In some experiments, indicated numbers of ALL-1 cells were resuspended in 25 μL IMDM containing 10% FBS, and injected with a microtiter syringe (Hamilton Co, Reno, NV) into human bone grafts implanted into SCID mice 8 weeks earlier. After 10 more weeks, the mice were killed, the human bone grafts removed, and single-cell suspensions prepared by mincing tissues with scissors in cold complete medium. Ammonium chloride treatment was then applied to lyse erythrocytes. Cellular DNA was extracted and subjected to PCR amplification, as previously described.

RESULTS

Irradiated TALL-104 cells lyse tumor targets, sparing normal cells. As measured in extended (18-hour) 51Cr-release assays, IL-2/IL-12-stimulated, γ-irradiated TALL-104 cells display high levels of cytotoxicity against a broad spectrum of tumor targets, including established hematopoietic (U937 and Raji), and nonhematopoietic (U-87 MG, A549, CHP-100, and WM1985) tumor cell lines (Fig 1A), and primary lymphoid (B- and T-ALL) and myeloid leukemia samples (Fig 1B and C). A great variability was observed in the lytic efficiency of irradiated TALL-104 cells against leukemic samples from different patients; however, all of the B-ALL or myeloid leukemias that were poorly sensitive to TALL-104 cell killing in a 51Cr release assay were growth arrested by 100% on a 3-day incubation with TALL-104 cells, as measured in 3H-TdR incorporation assays (not shown). Thus, these effectors can exert either cytotoxic or cytostatic effects on different leukemias. Growth inhibition was always accompanied by apoptotic cell death (not shown).

Importantly, normal cells, such as healthy melanocytes or cells derived from normal marrows and PB are completely resistant to TALL-104 cell killing (Fig 1D). Healthy donors' BM cells cultured in rh growth factors, such as IL-3 or GM-CSF, for 3 days and displaying high levels of proliferative activity are also resistant to TALL-104 cell lysis (Fig 1D). None of PB lymphocyte (PBL) and BM samples from the healthy donors tested were sensitive to the cytostatic effects of TALL-104 cells in 3H-TdR incorporation assays (not shown). To determine whether the failure of TALL-104 cells to lyse normal marrow cells was caused by binding defects, E/T conjugate assays were performed comparing the ability of TALL-104 cells to bind normal versus leukemic targets. As shown in Fig 2, TALL-104 cells can efficiently bind to U937 cells but are totally unable to form conjugates with normal BM cells. Competition experiments further confirmed that normal marrow cells do not compete for TALL-104 cell binding and killing of the leukemic targets U937 and Raji (Fig 3).

Cytokine production during TALL-104/BM incubation. Based on the ability of both nonirradiated and γ-irradiated TALL-104 cells to produce high levels of lymphokines when triggered by IL-2 or IL-12 or exposed to tumor targets, experiments were performed to measure possible cytokine release resulting from incubation of cytokine-TALL-104 cells with normal marrows. High levels of GM-CSF (10 ng/mL), IFN-γ (1,500 U/mL), and TNF-α (250 U/mL) were detected in the CM of IL-2/IL-12–stimulated, γ-irradiated TALL-104 cells admixed with healthy marrows for 18 hours (Fig 4). To determine the respective contributions of the two cell populations to cytokine production, TALL-104 cells, or BM cells, were pretreated for 4 hours with the protein synthesis inhibitors Actinomycin D and Puromycin, mixed with
the untreated BM, or TALL-104 cells, respectively, and incubated for 18 hours in the presence of rhIL-2 and IL-12. TALL-104 cells were the main producers of IFN-γ and GM-CSF whereas the two cell populations contributed equally to the production of TNF-α (Fig 4). Results of cytokine expression were in accordance with data of mRNA expression for IFN-γ, TNF-α, and GM-CSF by the two cell populations, shown in Fig 5. Specifically, the basal levels of all three cytokine mRNAs expressed by TALL-104 cells (lane 1) increased upon incubation with Actinomycin D/Puromycin-treated BM cells (lane 2); by contrast, BM cells did not express mRNA for any cytokine (lane 3) but TNF-α mRNA was detectable after a 4-hour incubation of these cells with Actinomycin D/Puromycin-treated TALL-104 cells.

Long-term effects of TALL-104 cells on normal hematopoietic progenitors in BM and cord blood samples. Two-week clonogenic assays were performed to exclude the possibility that the release of toxic mediators, such as TNF-α and IFN-γ (see Fig 4), would impair the growth of normal hematopoietic precursors in BM samples. Figure 6 shows that the clonogenic growth of committed (CFU-GM, BFU-E, and CFU-GEMM) progenitors in marrows from two donors admixed at various concentrations (0% to 50%) with TALL-104 cells was detectable after a 4-hour incubation of these cells with Actinomycin D/Puromycin-treated TALL-104 cells. TALL-104 cells did not affect the viability and long-term growth of pluripotent stem cells, nor of lineage-committed precursors.

Efficiency of lethally irradiated TALL-104 cells in purging sensitive and resistant leukemias. To test the efficacy of lethally irradiated TALL-104 cells in marrow purging different approaches were taken. In a first series of experiments, we tested purging efficacy against a target that is highly susceptible to TALL-104 cell killing: neo-R U937 cells were admixed at various concentrations (0% to 50%) with cells from normal BM. IL-2/IL-12–activated γ-irradiated TALL-104 cells were then added at the ratio of 1:1 relative to BM cells; the cell mixtures were incubated for 18 hours in the presence of DNase I, to digest DNA released by dying cells and, therefore, reduce false-positive results. PCR amplification of the neo-R gene 18 hours after addition of TALL-104 cells to BM/U937 samples showed the total disappearance of U937 cells from such samples at all E:T ratios used (Fig 7). Furthermore, no U937 cell colonies could be detected microscopically after a 2-week culture period in methylcellulose (not shown).

In a second set of experiments, we proceeded to determine whether TALL-104 cells would efficiently purge marrows infiltrated with lysis-resistant targets, such as the ALL-1 (pre-B) cell line. The susceptibility of this target to the cytotoxic/cytostatic effects of TALL-104 cells is shown in Fig 8A. Specifically, the killing efficiency of TALL-104 cells against ALL-1 cells is very low, even at high E:T ratios and...
in a long-term (18-hour) cytotoxic assay (no killing at all is observed in a 4-hour assay, data not shown). By contrast, in a 72-hour proliferation assay, irradiated TALL-104 cells can inhibit almost completely the growth of ALL-1 cells (Fig 8A). When ALL-1 cells were admixed at various concentrations (0% to 40%) with cells from normal marrows, and IL-2/IL-12-activated, γ-irradiated TALL-104 cells were added at the 1:1 ratio relative to BM cells for 18 hours, PCR amplification of the CDR3 specific region of ALL-1 cells always showed the presence of residual ALL-1 cells even when their initial concentration was 0.5% (Fig 8B). To determine whether the residual ALL-1 cells detected by PCR were tumorigenic on transfer into a human BM microenvironment, aliquots of unpurged and purged samples were injected into human fetal bone grafts previously implanted in SCID mice, and were allowed to expand for 2 months. Before injection in the fetal bones, both unpurged and purged samples were PCR+, although to a different extent (Fig 8C). Interestingly, PCR analysis of the cells recovered from the fetal bones 2 months later showed the local expansion of ALL-1 cells only from the unpurged mar-row (Fig 8D, lane 6). A known number of ALL-1 cells (from $2 \times 10^7$ to $10^8$) was injected in human bone grafts of a separate group of mice to measure the sensitivity of the system. The minimal number of ALL-1 cells that resulted in a PCR detectable growth in these grafts after 2 months was $2 \times 10^4$ (Fig 8D, lane 2).

**DISCUSSION**

Our previous studies have shown the ability of lethally irradiated TALL-104 cells to kill a broad range of malignant targets, including leukemias, with MHC nonrestricted mechanisms. We have also documented the antitumor efficacy of these potent effectors in SCID mice engrafted with human leukemia (U937 cell line) or glioblastoma (U-87 MG cells). These observations have prompted us to investigate the ability of irradiated TALL-104 cells to purge leukemic marrows ex vivo, with the idea that this might provide an alternate and highly effective marrow purging approach for potential clinical use in an autologous BMT setting.

Considerable controversy exists about the role of natural killer (NK) cells in the regulation of hematopoiesis.
been reported, in fact, that NK cells can either inhibit,33,34 stimulate,35,36 or not affect at all37 the growth of various hematopoietic progenitors. BM precursors appear to be more susceptible than PB progenitors to the inhibitory action of resting and IL-2–activated lymphocytes.38 Although TALL-104 cells kill tumors more potently than IL-2–activated lymphocytes (LAK cells), the present study shows that IL-2/IL-12–activated, γ-irradiated TALL-104 cells have little or no direct cytolytic activity against marrow cells from healthy donors, the mean lysis being always below 10%, even at high E:T ratios (100:1) in long-term (18 hour) 51Cr-release assays. This observation confirms studies done with LAK cells in rats39 and humans.40 Importantly, E:T conjugate formation assays and competitive inhibition experiments both showed that the failure of TALL-104 cells to lyse normal marrow cells was due to binding defects, ie, to the inability of these effectors to recognize and physically interact with this type of target. These results are in accordance with another study on LAK cells.41

The lack of direct cytotoxicity of TALL-104 cells against normal hematopoietic elements is a necessary condition for the possible applicability of these killer cells in a clinical setting of BM purging. The ability of TALL-104 cells to actually distinguish leukemic progenitor cells from normal progenitors in the same individual, thus killing only the malignant blasts and sparing healthy hematopoietic elements, is very difficult to show at the molecular level, because of both the scarcity of PCR reagents specifically detecting different leukemia subsets, and the intrinsic limitations of the PCR technology. In fact, the sensitivity of PCR detection is always below one out of 106 cells and, as discussed below, a PCR-positive result may very well reflect a state of irreversible quiescence induced by TALL-104 cells in certain types of leukemias. To address the crucial issue of whether TALL-104 cells spare normal progenitors, we used two approaches. One approach was to examine the clonogenic potential of BM cells from a relatively large number of healthy donors on incubation with the irradiated effectors. We found that in long-term (2-week) clonogenic assays, BM cells from 10 normal individuals preincubated with IL-2/IL-12–activated, γ-irradiated TALL-104 cells for 4 or 18 hours at E:T ratios of 0.1:1 and 1:1 were able to form colonies (CFU and BFU) at the same extent as control marrows. The second approach was to examine the effects of TALL-104 cells on CD34–positively selected cells from human umbilical cord blood samples, which compared with adult human marrow, are a rich source of hematopoietic stem and progenitor cells.27 An early CD34+ cell population with very high proliferative and replating potential was recently isolated from human umbilical cord blood by Lu et al.27 These colony-forming cells are present in about eightfold higher frequency in cord blood than in adult BM and appear to be associated with the high hematopoietic repopulating capacity of umbilical cord blood cells.27 Our data with CD34-enriched cord blood samples show the failure of TALL-104 cells to reduce the number of any type of colony forming cells detectable in a 14-day clonogenic assay, including the CFU-GEMM. This type of CFU morphologically resembled the human early progenitors with high-proliferative potential found in cord blood samples27 and we were able to replate them at least 4 times. These data confirm that TALL-104 cells do not affect the self-renewal potential of very early hematopoietic precursors.

Based on the negative effects of IFN-γ and TNF-α on the clonogenic growth of hematopoietic cells,33,34 and on the ability of TALL-104 cells to produce high levels of these
cytokines upon exposure to IL-2, IL-12, or tumor targets, we also investigated, in this study, whether in the absence of a direct lytic activity, TALL-104 cells could still exert inhibitory effects on the growth of hematopoietic precursors through the release of toxic mediators. Interestingly, we found that normal BM cells are able to produce TNF-α during an 18-hour incubation with TALL-104 cells, thus indicating that there is a subpopulation in nonleukemic, healthy marrows that recognizes TALL-104 cells as foreign stimulus and responds to it by producing cytokines.

The absence of inhibition of CFU growth, even in the presence of high levels of endogenous TNF-α and IFN-γ (as indicated in Fig 4), could be attributed to the antagonizing activity in the same milieu of GM-CSF, another cytokine produced by activated TALL-104 cells, which has potent stimulatory effects on marrow progenitors. Altogether, these results indicate that TALL-104 cells do not affect the viability and long-term growth of pluripotent stem cells and lineage-committed precursors, and are in accordance with other data in the literature showing the lack of inhibitory effects by other MHC nonrestricted effectors (both CD3/TCR-γδ+ and -αβ T-cell clones) against the same cells. These data indicate that there is a subpopulation in nonleukemic, healthy marrows that recognizes TALL-104 cells as foreign stimulus and responds to it by producing cytokines.

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are further supported by findings in rats, in which marrow grafts pretreated with LAK cells retained the ability to reconstitute lethally irradiated recipients. Our recent findings in the B6D2F1 murine model of syngeneic 70Z pre-B cell leukemia provide strong evidence that heavily infiltrated leukemic marrows from these animals, cultured for 18 hours with irradiated TALL-104 cells retain the ability to fully reconstitute lethally irradiated recipients without inducing leukemia (Cesano et al., manuscript in preparation). These data in an animal model strongly support the ability of TALL-104 cells to effectively purge leukemic marrows without affecting the repopulating potential of early marrow precursors. Experiments are underway to extend these findings to human CD34⁺ marrow and cord blood progenitors by examining their ability to reconstitute SCID mice after TALL-104 purging.

Table 1. Clonogenic Potential of Cord Blood-Derived CD34⁺ Cells After Incubation With TALL-104 Cells

<table>
<thead>
<tr>
<th>TALL-104/CD34 Ratio</th>
<th>CFU-E</th>
<th>BFU-E</th>
<th>CFU-GM</th>
<th>CFU-GEMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:1</td>
<td>43 ± 1</td>
<td>538 ± 63</td>
<td>1,418 ± 115</td>
<td>32 ± 21</td>
</tr>
<tr>
<td>1:1</td>
<td>56 ± 22</td>
<td>732 ± 183</td>
<td>1,617 ± 61</td>
<td>44 ± 0</td>
</tr>
</tbody>
</table>

10⁶ CD34 positively selected cells from a cord blood sample were incubated alone or with irradiated TALL-104 cells for 18 hours, and then subjected to a 14-day colony assay. Both purged and unpurged CFU-GM and CFU-GEMM could be replated 2 and 4 more times, respectively. No toxic effects on colony formation were seen with CD34 cells positively selected from two more cord blood samples.
After establishing the lack of direct and cytokine-mediated toxicity of TALL-104 cells on normal hematopoietic elements, experiments were designed to test the purging efficacy of these effectors against lysis-susceptible and -resistant leukemic targets admixed with healthy marrows. In the case of leukemic targets displaying high susceptibility to MHC nonrestricted lysis (such as U937 cells), TALL-104 cells were able to completely eliminate all the leukemic cells, even when present at 50% concentration in the marrows, as measured both by PCR amplification of the neo-R marker gene, and by long-term clonogenic assays. By contrast, when a more resistant leukemic target was used, such as the ALL-1 cell line, TALL-104 cells were not able to eliminate them, as shown by both 51Cr-release assays and PCR, even when marrow contamination was limited to 1.5%. Because, however, TALL-104 cells can inhibit almost completely the growth of most resistant leukemias, including ALL-1 cells, as measured in 3H-TdR incorporation assays, we wanted to determine whether the PCR technique was giving false-positive results by simply identifying growth arrested ALL-1 cells that would eventually become apoptotic. To prove this point, in vivo experiments were performed to test whether PCR detected ALL-1 cells had maintained their tumorigenicity in vivo. SCID mice engrafted with human fetal bones were chosen as a model system because it allows the growth of most human leukemic cells in a human marrow microenvironment and the expansion of very low numbers of freshly separated human leukemias.31

Results showing the failure of TALL-104-purged marrows, which were PCR− for ALL-1 cells, to induce leukemia in this immunodeficient host demonstrated that the residual ALL-1 cells were, at the moment of the injection, either dying or permanently unable to further proliferate. These results are conceptually very important as they introduce a word of caution in interpreting PCR data. Namely, the PCR technique, although excluding necrotic cells, does detect cells that are either growth arrested or in a pre-apoptotic phase. Therefore, a PCR-positive result after purging with any biologic agent does not necessarily indicate a failure of the purging procedure, but may indicate that the applied treatment has impaired the growth or tumorigenic potential of the target. Likely, under certain conditions, PCR detectable residual malignant cells may even be eliminated by the host’s immune system.

In conclusion, the data presented in this report indicate the ability of irradiated TALL-104 cells to eliminate malignant blasts either by cytotoxic or by cytostatic mechanisms, yet sparing normal hematopoietic precursors. This creates an advantageous therapeutic index for this human killer clone in
potential marrow purging strategies and even in consolidative immunotherapy in combination with autologous BMT. Importantly, in addition to leukemias and lymphomas, this approach might be feasible for eradicating residual disease in other forms of cancer displaying BM involvement, including neuroblastoma in children and breast carcinoma in adult patients, whenever treatment with high-dose chemotherapy or radiotherapy followed by rescue BMT is indicated.

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REFERENCES


Use of a lethally irradiated major histocompatibility complex nonrestricted cytotoxic T-cell line for effective purging of marrows containing lysis-sensitive or -resistant leukemic targets [see comments]

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