Efficacy and Safety of Simultaneous Immunomagnetic CD34+ Cell Selection and Breast Cancer Cell Purging in Peripheral Blood Progenitor Cell Samples Used for Hematopoietic Rescue after High-Dose Therapy

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ABSTRACT

We have established a new simultaneous positive/negative selection procedure using the Baxter Isolex 300i system. We tested its tumor cell (TC) purging efficacy by tumor contamination tests ex vivo and its safety in a group of 17 breast cancer (BC) patients by measuring hematopoietic recovery after high-dose (HD) therapy and autologous stem cell rescue with the selected cells. Tumor contamination tests resulted in a TC depletion of 4.1–6.0 log steps. The CD34+ cell yield in this experimental setting was 38.9–91.5%, and the CD34+ cell purity was 86.0–96.0%. In a group of 17 BC patients (5 high-risk adjuvant, ≥10 lymph nodes positive, and 12 metastatic), we processed leukapheresis products (LPs) by simultaneous positive/negative selection. In these clinical samples, the mean CD34+ cell yield was 56.2% (range, 14.0–80.1%), and the CD34+ cell purity was 94.5% (range, 69.0–99.8%). Additionally, we screened samples of the patients’ LPs before and after the purging procedure for contaminating TC by immunocytochemistry. In 15 of 17 tested cases, TCs were detectable prior to the purging procedure. After the procedure, we could not detect residual TCs in 16 of 17 cases. In one case, we found a highly reduced number of TCs. Furthermore, we evaluated the times for hematopoietic reconstitution in a group of five BC patients in the high-risk adjuvant situation who underwent HD chemotherapy and hematopoietic rescue with positive/negative selected stem cells and compared it with our own data from 10 BC patients who, after identical HD therapy, received only positively selected CD34+ cells and 14 patients who, after identical HD therapy, received autografts purged by incubation with toxic ether lipids (ET-18-OCH3). In all groups, a leukocyte count of >2000 cells/μl was reached at day +10. A platelet count of >50,000 cells/μl was reached at day +12 in the ET-18-OCH3 group and at day +14 in the other two groups. Furthermore, 12 patients with metastatic disease rescued with positive/negative selected stem cells after HD therapy also showed fast and comparable hematopoietic recovery. The new simultaneous immunomagnetic positive/negative selection using a closed system is effective and safe. Processing LPs leads to a similar CD34+ cell yield, a higher TC depletion compared to standard CD34+ cell selection, and no delay in hematopoietic recovery.

INTRODUCTION

Several Phase III studies showed that HDC3 with stem cell support was more beneficial than conventional therapy in malignant diseases such as acute myelogenous leukemia (1), Hodgkin’s disease (2), lymphoma (3, 4), myeloma (5), and BC (6). PBPCs have nearly replaced BM as a source of autologous hematopoietic stem cells used for hematopoietic rescue after HDC. The use of PBPCs instead of BM leads to a faster hematopoietic recovery (7–9), contributing to feasibility and lower lethality of HD protocols. Additionally, TC contamination has been described by some authors as being lower in PBPCs than in BM samples (10).

In recent years, BC became an important area for studying PBPC transplantation following HDC (6, 11). The high prognostic value of BM micrometastases (12) and the mobilization of these cells into the peripheral blood following priming for PBPC collection are well known (13–15). Diel et al. (12) showed that, at the time of surgery, BM micrometastases could be found in 31% of node-negative patients and that the BM status is an independent prognostic factor with a prognostic value higher than that of the nodal status.

Retrospective studies indicate that TC contamination of stem cell autografts may be an important factor for the prognosis of BC, Hodgkin’s disease, lymphoma, and acute myelogenous leukemia patients after HD therapy and retransfusion (16–19).
Direct evidence for a relapse caused by contaminating TCs was presented by gene-marking studies in leukemia and neuroblastoma (20–22). Although their negative influence on the clinical outcome after stem cell retransfusion is still not proven by randomized prospective Phase III studies, the reduction of residual TCs is a main target of LP processing. A large number of depletion methods have been developed (23). Immunomagnetic CD34+ cell enrichment (selection) is a widely applied and effective purging procedure (14, 24). An additional purging effect can be achieved by combination with a second negative immunomagnetic step directed toward the removal of TCs (25, 26). However, these sequential techniques are expensive and time consuming and lead to a low CD34+ cell yield.4

This is the first report of a simultaneous immunomagnetic double purging procedure (positive/negative or +/- selection) for LPs from BC patients using new selective removal devices in the Isolex 300i system.

MATERIALS AND METHODS

Patient Characteristics and Therapy. We performed the simultaneous +/- purging procedure for LP of a group of 17 BC patients (5 high-risk adjuvant, ≥10 lymph nodes positive, and 12 metastatic). PBPC collection was performed with a Cobe Spectra cell separator (Cobe, Heimstetten, Germany) in the 5 high-risk adjuvant patients after the third of four cycles of 90 mg/m^2 epirubicin-600 mg/m^2 cyclophosphamide and 10 μg per day of s.c. G-CSF (filgrastim; Amgen, Thousand Oaks, CA) and in the 12 metastatic patients after the fifth of six cycles of 90 mg/m^2 epirubicin-135 mg/m^2 paclitaxel and 10 μg per day of G-CSF. Within 12–14 days following chemotherapy, the CD34+ cell counts, as monitored daily in the peripheral blood, reached numbers higher than 10 cells per μl. In 16 patients, one single PBPC collection was needed, and in 1 patient, two PBPC collections were needed to reach CD34+ cell numbers of ≥5 × 10^6 cells/kg prior to cell processing.

Five of the patients after 90 mg/m^2 epirubicin-600 mg/m^2 cyclophosphamide plus G-CSF mobilization (high-risk adjuvant) and 12 of the patients after 90 mg/m^2 epirubicin-135 mg/m^2 paclitaxel plus G-CSF mobilization (metastatic) were treated with HD therapy and stem cell rescue. HD therapy consisted of cyclophosphamide (6 g/m^2), thiotaite (600 mg/m^2), and mitoxantrone (40 mg/m^2) for the 5 high-risk adjuvant patients and of cyclophosphamide (6 g/m^2), thiotaite (500 mg/m^2), and carboplatin (800 mg/m^2) for the 12 metastatic patients. This was followed by stem cell rescue with simultaneously +/- purged CD34+ cells and daily G-CSF (filgrastim; 10 μg/m^2).

The PBPC collection of the high-risk adjuvant patients in the two retrospective control groups, consisting of 14 patients retransfused with PBPCs purged by incubation with toxic ether lipids (75 μg/ml ET-18-0CH₄ for 4 h) as described (27, 28) and 10 patients treated with CD34+ enriched stem cells (+ selection only), showed identical demographics and disease characteristics (age, stage, prior therapy, and performance) and underwent the identical HD therapy within the same study protocol.

Patients were entered on trial only after informed consent was obtained. Study protocols were approved by the institutional human investigations committee.

Flow Cytometry. CD34+ hematopoietic cells were quantified by three-color immunofluorescence using a FACScan flow cytometer (Becton Dickinson, San Jose, CA) with the assistance of CellQuest software. The following antibodies were used: CD34-PE, CD45-FITC (Becton Dickinson), and CD64-FITC (Medarex, Annadale, NJ). For viability testing after cryopreservation, propidium iodide was added as a third fluorescent compound.

Purging Procedure. After storage of the collected cells of the LPs (culture medium: human serum albumin (HSA), 1:1, 4°C, for a maximum of 48 h) the immunomagnetic CD34+ cell enrichment (Isolex 300i, standard set and software; Baxter, Munich, Germany) was performed (temperature of <25°C) as described by the manufacturer, with the following modifications. During the procedure, following the transfer of a new specific competitive stem cell-releasing agent (PR34+; Baxter) to the separation column, we added MoAbs against BC glycoproteins (Mr, 42,000, 55,000, and 200,000; Baxter) bound to Immunobeads (Dynabeads M450; Dynal, Ost, Norway) for additional negative selection of TCs (29). To avoid cell clumping, during the procedure, we prefilled the separation column with 2500 units of Pulmozyme (Roche, Grenzach, Germany) plus 1.0 mmol of MgCl₂ per 1 × 10^10 cells.

Evaluation of Immunomagnetic CD34+ Cell Selection. The efficiency of the immunomagnetic separation procedure to select CD34+ cells from peripheral blood mononuclear cells (+ selection) was evaluated by applying definitions as published previously (24):

\[ \text{Purity} = \frac{\text{Total count of CD34+ cells in the positive fraction}}{\text{Total count of CD34+ cells in the starting suspension}} \times 100 \]

The TCD was expressed as described below.

The cell product was cryopreserved after +/- selection with computer assistance at a rate of ~1°C/min and stored in liquid nitrogen until retransfusion. Extra vials were frozen for quality control. The following parameters were tested after thawing: (a) number and purity of CD34+ and propidium iodide-negative (viable) cells; (b) viability and cell count in trypan blue; (c) colony count in a colony-forming unit assay (Methocult H4431; Stemcell Technologies, Vancouver, British Columbia, Canada); and (d) microbiological sterility control.

Storage of CD34+ cell-enriched or ether lipid-purged cells for the control groups was identical.

Immunocytochemical Staining. Aliquots of the cell suspensions were investigated before and after the purging procedure for contaminating TCs by microscopy after cytoarin preparation and immunocytochemical staining (Epimet-Epithe-lian Cell Detection Kit; Micromet, Munich, Germany). Cells were centrifuged on glass slides at a density of 2000 cells per mm². The detection method is based on the reactivity of the murine MoAb A45-B/B3 linked to alkaline phosphatase with the cell cytoskeleton after membrane permeabilization. This MoAb has no cross-reactivity with the MoAbs used for selection. Cytokeratin positive cells show a new fuchsin red color

4 Submitted for publication.
after staining. We stained $1 \times 10^7$ cells from the LP and the purged fraction. If no TCs were detectable, an immunomagnetic enrichment (Dynabead-Anti Epithelial Cell; Dynal) was performed of $1 \times 10^8$ cells (only from LPs), and the staining procedure was repeated on cytopsins with enriched TCs. The general sensitivity of the method thus is in excess of 1 TC per $1 \times 10^6$ cells. Details can be deduced from Table 1.

**TC Contamination Experiments.** In an experimental setting, we evaluated the purging efficacy of our simultaneous +/- selection method by contamination of $10 \times 10^6 - 50 \times 10^6$ cells of LP from patients without diagnosis of epithelial tumors (informed consent of the patients was obligatory for using surplus cells from their LPs for these experiments) with the human BC cell lines HTB 22, HTB 131, and HTB 19 (American Type Culture Collection, Manassas, VA) at TC concentrations of 0.5 and 5%. The contaminated LP was processed in the same way as described for the clinical samples. TCs were detected before and after simultaneous +/- purging. The TCD was expressed in log steps as follows:

$$ \text{log depletion} = \log \left( \frac{\text{No. of TCs in the starting fraction}}{\text{No. of TCs in the selected and purged fraction}} \right) $$

Considering that, in this calculation, a bad CD34+ yield would be expressed as additional TCD, we decided to calculate with the “yield-corrected” TCD:

Yield corrected TCD [log]

$$ = \text{TCD [log]} - \log \left( \frac{1}{\text{CD34+ cell yield}} \right) $$

Thus, all TCD values presented in this report are yield corrected. Cells were not used again after completion of the experiment.

**RESULTS**

In this series of experiments we have established and tested a new simultaneous immunomagnetic double purging procedure (+/- selection) for LPs from BC patients using new selective removal devices in the Isolex 300i system.

**Purging Procedure.** In the clinical application, using LPs from 17 BC patients, simultaneous immunomagnetic +/- selection led to a mean CD34+ cell purity of 94.5% (range, 69.0–98.9%). The mean yield of CD34+ cells was 56.2% (range, 14.0–80.1%). In two cases, extremely bad yield and purity was caused by clumping during magnetic separation. We could avoid this problem successfully later on by working at room temperatures of $<25^\circ$C during the procedure and adding Pulmozyme to the column, as described in “Materials and Methods.”

In 15 of 17 tested samples, we could detect TCs prior to the purging procedure (Table 1). After purging, a reduced number of TCs were detectable only in 1 case (Table 1).

**Hematopoietic Recovery.** Five of the high-risk adjuvant and 12 of the metastatic patients were treated with HDC as described above, followed by stem cell rescue with simultaneously +/- selected CD34+ cells (target, $>1 \times 10^6$ CD34+ cells per kg). The hematopoietic recovery times are given in Tables 2 and 3. All patients recovered hematopoiesis (normal blood cell counts) promptly.

**Control Groups.** To show possible negative effects of the new +/- purging procedure on CD34+ cell yield and time to engraftment, we retrospectively compared the data from the 5 high-risk adjuvant patients with our own data from 24 high-risk adjuvant patients who received PBPCs that were processed differently but received identical mobilization and HD therapy within the same study protocol (Table 2). There were no relevant differences detectable in the data for CD34+ cell yield, CD34+ cell purity, and hematopoietic recovery between the +/- selection group and the group whose LPs were CD34+ cell enriched only (+ selection; see Table 2). The patients who were retransfused with ET-18-OCH$_3$-purged PBPCs received a $>50\%$ (mean) higher number of CD34+ cells and reached platelet counts of $>50,000$ cells/$\mu$L 2 days earlier (Table 2).

**Purging Efficacy.** Surplus cells from LP of four donors with diagnosis other than epithelial tumor and normal BM cytology were contaminated with cells from human BC cell lines. In the following experimental simultaneous +/- selection runs, the mean yield of CD34+ cells was 70%, and the mean CD34+ cell purity was 92.8%. The yield-corrected TCD ranged between 4.1 and 6.0 log steps (Table 4). Compared with positive CD34+ cell selection only or pharmacological purging by ET-18-OCH$_3$, the TCD was 2–3 log steps higher (24, 30). The excellent CD34+ cell yield in these tests may be caused by the lower number of cells processed ($1 \times 10^{10}$ cells) in three of the tests compared to the clinical samples (up to $8 \times 10^{10}$ cells).

Furthermore, 15 of 17 patients of our clinical patient group, we could detect TCs in the LP prior to the purging procedure. After purging, TCs were detectable only in 1 case, at a considerably reduced number. The estimated depletion rates for 10 patients with a contamination rate of $>1$ TC per $10^6$ MNC prior to processing ranged between >2.1 and >3.6 log steps (Table 1). In the only case in which we could detect TCs before and after processing, the yield-corrected TCD was 2.5 log steps (Table 1). No TCs were detectable in two cases and a very low contamination rate ($<1$ TC per $10^6$ MNCs) was observed in four cases, who could not be further evaluated after processing due to minimum cell numbers required for clinical stem cell rescue in these patients (not evaluable in Table 1).

**Table 1  Clinical TCD results**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Before processing$^a$</th>
<th>After processing$^b$</th>
<th>TCD (log)</th>
<th>Yield-corrected TCD (log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$6 \times 10^4$</td>
<td>0 (&lt;1/1 x 10$^5$)</td>
<td>&gt;3.0</td>
<td>&gt;2.8</td>
</tr>
<tr>
<td>2</td>
<td>$10 \times 10^4$</td>
<td>203</td>
<td>2.7</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>$14.8 \times 10^4$</td>
<td>0 (&lt;1/1 x 10$^5$)</td>
<td>&gt;3.6</td>
<td>&gt;3.4</td>
</tr>
<tr>
<td>4</td>
<td>$8.5 \times 10^4$</td>
<td>0 (&lt;1/1 x 10$^5$)</td>
<td>&gt;3.6</td>
<td>&gt;2.8</td>
</tr>
<tr>
<td>5</td>
<td>$11.4 \times 10^4$</td>
<td>0 (&lt;1/1 x 10$^5$)</td>
<td>&gt;3.6</td>
<td>&gt;3.2</td>
</tr>
<tr>
<td>6</td>
<td>$14.6 \times 10^4$</td>
<td>0 (&lt;1/1 x 10$^5$)</td>
<td>&gt;3.7</td>
<td>&gt;3.6</td>
</tr>
<tr>
<td>7</td>
<td>$2.7 \times 10^4$</td>
<td>0 (&lt;1/1 x 10$^5$)</td>
<td>&gt;3.1</td>
<td>&gt;2.9</td>
</tr>
<tr>
<td>8</td>
<td>$8.2 \times 10^4$</td>
<td>0 (&lt;1/1 x 10$^5$)</td>
<td>&gt;3.7</td>
<td>&gt;3.4</td>
</tr>
<tr>
<td>9</td>
<td>$1.6 \times 10^4$</td>
<td>0 (&lt;1/1 x 10$^5$)</td>
<td>&gt;2.4</td>
<td>&gt;2.1</td>
</tr>
<tr>
<td>10</td>
<td>$37 \times 10^4$</td>
<td>0 (&lt;1/1 x 10$^5$)</td>
<td>&gt;3.9</td>
<td>&gt;3.4</td>
</tr>
</tbody>
</table>

$^a$ Total no. of TCs per LPs.

$^b$ Total no. of TCs in the +/- selected product.
immunomagnetic Double Purging of Tumor Cells

Table 2 Comparison of clinical purging results in high-risk adjuvant patients

<table>
<thead>
<tr>
<th>Method</th>
<th>n</th>
<th>CD34+ yield (%)</th>
<th>CD34+ purity (%)</th>
<th>CD34+ cells/kg</th>
<th>WBC count of &gt;2,000/μl (day)</th>
<th>Platelet count of &gt;50,000/μl (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-18-OCH3</td>
<td>14</td>
<td>NE</td>
<td>NE</td>
<td>8.5 x 10^6</td>
<td>10.6 (7–28)</td>
<td>11.8 (8–33)</td>
</tr>
<tr>
<td>+ selection</td>
<td>10</td>
<td>49.3 (20.9–75.7)</td>
<td>95.5 (92–98)</td>
<td>3 x 10^6</td>
<td>10.1 (8–11)</td>
<td>13.5 (10–16)</td>
</tr>
<tr>
<td>+/- selection</td>
<td>5</td>
<td>51.1 (14–68)</td>
<td>92 (61–99.8)</td>
<td>3.9 x 10^6</td>
<td>10.2 (9–11)</td>
<td>13.8 (12–15)</td>
</tr>
</tbody>
</table>

* Values are means (ranges).

Table 3 Clinical purging results in patients with metastatic disease

<table>
<thead>
<tr>
<th>n</th>
<th>CD34+ purity (%)</th>
<th>CD34+ yield (%)</th>
<th>CD34+ cells/kg</th>
<th>Platelet count of &gt;50,000/μl (day)</th>
<th>WBC count of &gt;2,000/μl (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>95.2 (85–99.5)</td>
<td>58.3 (32–80.1)</td>
<td>2.1 x 10^6</td>
<td>13.6 (12–17)</td>
<td>11.7 (11–13)</td>
</tr>
</tbody>
</table>

* Values are means (ranges).

Table 4 Experimental purging results

<table>
<thead>
<tr>
<th>Test no.</th>
<th>Contamination</th>
<th>CD34+ yield (%)</th>
<th>CD34+ purity (%)</th>
<th>TCD (log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 x 10^6 MNCs + 5% HTB 131</td>
<td>73.6</td>
<td>90</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>10 x 10^6 MNCs + 0.5% HTB 22</td>
<td>91.5</td>
<td>96</td>
<td>4.1</td>
</tr>
<tr>
<td>3</td>
<td>50 x 10^6 MNCs + 0.5% HTB 19</td>
<td>38.9</td>
<td>86</td>
<td>4.54</td>
</tr>
<tr>
<td>4</td>
<td>10 x 10^6 MNCs + 0.5% HTB 22</td>
<td>75.0</td>
<td>99</td>
<td>4.14</td>
</tr>
</tbody>
</table>

DISCUSSION

The clinical relevance of TCs purging from hematopoietic stem cell autografts prior to reinfusion after HD therapy is still an open question. Randomized studies dealing with this problem do not exist thus far. However, gene-marking studies, case reports, and the well-known fact that, even in remission, occult TCs can be detected in BM and peripheral blood argue in favor of the application of purging procedures (20–23, 31). Thus, different purging methods have been developed (23, 24, 29, 30–32).

In this study, we have examined the safety and efficacy of purging PBPCs from BC patients by using a new simultaneous immunomagnetic +/- selection. Using LPs from 17 BC patients, clinical-scale simultaneous immunomagnetic +/- selection led to a mean CD34+ cell purity of 94.5% and a mean yield of CD34+ cells of 56.2%. This is comparable with previous results using similar immunomagnetic devices for CD34+ cell selection only (24, 33, 34). Hematopoietic recovery of BC patients after HD therapy and stem cell rescue was prompt, and no major delay was observed comparing patients retransfused with LP after +/- selection, CD34+ cell enrichment only, or chemical purging with toxic ether lipids. Although this was a retrospective comparison, we consider it as being of clinical relevance because the patients of all three groups compared showed matched demographics and were treated on the same study protocol with identical inclusion/exclusion criteria and identical HD therapy and, thus, because these groups of patients represent control groups for positive stem cell selection and negative TC purging only.

Purging efficacy was evaluated clinically and 15 of 17 tested patients contained detectable TCs in their LP prior to the purging procedure, whereas after purging, TCs were detectable only in 1 case. The absence of residual TCs in all but one probe after processing complicates the evaluation of the clinical purging efficacy, and we are only able to give minimum purging efficacy in log steps ranging between >2.1 and >3.6 log steps (Table 1). In only one single case could we detect TCs before and after double purging with the purging efficacy being 2.5 log steps in this patient with high contamination. Furthermore, purging efficacy was also tested experimentally by spiking LPs from donors with human BC cell lines. For these experiments, we used clinical-scale volumes and cell numbers, and the yield-corrected TCD ranged between 4.1 and 6.0 log steps. However, although we have performed clinical-scale experiments, these results must be interpreted with due caution because lower TC contamination rate in the actual clinical situation may influence the purging efficacy.

Today, there are three main different purging methods that are used clinically, which are still intensively tested for methodological improvement and clinical relevance. Apart from positive stem cell selection (e.g., immunomagnetically with anti-CD34 antibodies), there are negative selection techniques in which TCs are eliminated either immunologically by antitumor antibodies or chemically pharmacologically by toxin or drug exposure (16, 17, 35–39).

Choosing a positive stem cell selection system offers multiple advantages. CD34+ hematopoietic cells can be enriched up to >90% (our data) before retransfusion into the patient. This means less volume, less freezing medium, and, therefore, less potential toxicity for the patient. CD34+ cells of LP show a full
capability of restoring hematopoiesis when administered following HD therapy (40) and identical reconstitution of hematopoiesis as with unseparated LP (41). However, immunomagnetic CD34+ cell selection can decrease TC numbers by only 1.9–2.75 log steps as reported previously (14, 24) with 3.1 log steps being at the upper end of purging efficacy, as reported in a randomized myeloma trial (42).

On the other hand, negative selection techniques bear the risk of purging damages for hematopoietic stem cells (36, 43). Some studies show depletion of normal hematopoietic cells, delay in engraftment, and an increasing risk of myelosuppressive complications. This can be due to simultaneous toxic effects by chemotherapeutics and immunotoxins on hematopoietic precursor cells. In addition, the efficiency of chemically purging BC cells in vitro with 4-hydroperoxycyclophosphamide is with 1–2 log step depletion (32), similar to the procedure with ether lipids, and subsequent cryopreservation (30) and has only low efficacy. Removal of 1–4 log steps of TCs with one purging cycle was seen when using a cocktail of three different antitu- mor antibodies (38). Anderson et al. (32) combined immunomagnetic purging with 4-hydroperoxycyclophosphamide and eliminated up to 5 log steps of clonogenic BC cells, but with a reduced recovery (<50%) of granulocyte macrophage colony-forming units.

The BC purging method described here for the first time combines positive CD34+ cell enrichment with negative TC purging by a simultaneous immunomagnetic procedure using a closed system. Its safety and efficacy compare favorably with the other techniques published previously. It is as easy to perform as the positive selection of CD34+ cells with the same system, and costs are only increased by ~20%. We recommend simultaneous immunomagnetic double purging for clinical application within further study protocols with purging as a study objective.

ACKNOWLEDGMENTS

The excellent technical assistance of Birgit Reufi and Carola Mücke is gratefully acknowledged.

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