Minimal Residual Cancer Detection in Hematopoietic Stem Cell Products and Its Prognostic Significance in Patients With Breast Cancer, Lymphoma, or Multiple Myeloma

Thomas J. Moss, MD

The effect of contaminating tumor cells in the stem cell product on relapse remains an area of active clinical investigation.

Background: Despite the initial success of high-dose therapy and bone marrow transplant, the major reason for posttransplant failure is relapse of disease. Reinfusion of tumor cells may contribute to relapse in autologous stem cell transplants. We now have ultra-sensitive methods of tumor cell detection that can determine the presence of minimal residual cancer (MRC) in marrow and peripheral blood stem cells.

Methods: The author has conducted a critical review of the literature on this issue.

Results: The factors that are associated with an increase in contamination of the graft include (1) the number of cycles of induction therapy, (2) the type of mobilization regimen used, (3) the presence of tumor cells in the marrow, and (4) the number of phereses. A number of studies show that the presence of occult breast cancer in the marrow and/or stem cell product predicts for a poor posttransplant clinical outcome. The presence of clonogenic breast cancer or lymphoma cells in the graft is also associated with a very poor outcome. Published data regarding contamination in graft and outcome for patients with myeloma are limited.

Conclusions: Testing for minimal MRC in the oncology patient provides prognostic information that may be useful to the transplant physician.

Introduction

Autologous bone marrow/stem cell transplant (HSCT) following high-dose therapy is being used with increasing frequency for patients with breast cancer, multiple myeloma, and non-Hodgkin’s lymphoma. Despite the initial success of this therapy, the major reason for posttransplant failure is relapse of disease. A patient may relapse for multiple reasons, such as a high in vivo tumor burden, the development of drug resistance, the lack of an tumor immune response by the patient’s hematopoietic cells, or reinfusion of malignant cells that contaminate stem cell products. The exact contribution of each mechanism toward a relapse is uncertain at this time. Reinfusion of tumor cells may contribute to relapse in autologous stem cell transplant patients. Hence, the detection and quantitation of the minimal residual cancer (MRC) cells both in vivo and in the graft may be helpful in determining the prognosis of individual patients. We now have ultra-sensitive methods of tumor cell detection that can determine the presence of MRC in marrow and peripheral blood stem cells (PBSC). This new technology allows us to determine the incidence and clinical significance of MRC in the HSCT patient. The purpose of this manuscript is to provide a comprehensive clinical review of MRC data currently reported in the literature. This includes a review of numerous clinical issues regarding tumor cell contamination of stem cell/marrow grafts. These issues include (1) the incidence of tumor cell contamination in stem cell products, (2) the factors that affect the incidence of contamination, (3) the effect of cytokines on the mobilization of tumor cells, (4) the association of marrow disease with the risk of relapse after HSCT, (5) the clinical significance of tumor cells in the graft, and (6) the use of stem-cell isolation platforms (eg, CD34 selection devices, ex vivo expansion) for purging tumor cells from the stem cell product.

Detection of MRC

Detection of MRC in marrow or PBSC using routine histology and cytology has a low sensitivity of detecting tumor cells (Fig 1). Since identification of metastatic disease is based solely on cellular morphology, single tumor cells and/or small clumps of malignant cells may go unappreciated by the pathologist.
We now have new methodologies such as immunocytochemistry (ICC) and polymerase chain reaction (PCR) that can sensitively detect MRC (eg, 1 tumor cell among 1,000,000 normal hematopoietic cells).\(^1,2\) ICC testing utilizes monoclonal antibodies that bind to tumor antigens but not to normal hematopoietic antigens. For accurate and sensitive detection, antibodies are chosen on the basis of affinity for tumor cells, absence of binding to normal marrow cells, and location of antigen (cytoplasm or cell surface membrane). PCR testing uses probes that identify unique gene sequences present within the genome of the malignant cell. To date, the best unique gene sequences are caused by a translocation. In addition, reverse transcription PCR (RT-PCR) offers the opportunity to use reverse transcriptase to identify the mRNA expression of tumor-specific gene products to identify the presence of solitary malignant cells. With the use of these newer, more sensitive methods of tumor detection, we now know that occult bone marrow metastases occur frequently regardless of the malignancy (breast cancer, lymphoma, multiple myeloma, etc).\(^3,4\)

The ICC method involves a cytocentrifuge preparation of marrow or PBSC cells where visualization of bound antibody is ultimately achieved by a chemical reaction between an enzyme and coloring agent (Fig 2). This method requires a great deal of technical expertise to be performed correctly and can be time consuming to perform. However, it is superior to fluorescent-based detection methods because sensitivity and specificity of detection can be verified by morphologic evaluation of immunostained cells. Alkaline phosphatase staining methods appear to be the most widely used and have a sensitivity varying from 1 tumor cell among 10\(^5\) normal cells down to 1 tumor cell among 10\(^6\) cells.\(^1,2,4\) With newer tumor enrichment methods, the sensitivity of this method can routinely be 1 tumor cell among 10\(^7\) normal cells.\(^5\) This method has become the gold standard for evaluation of minimal residual disease in marrow and stem cell products for patients with breast cancer.

PCR is another sensitive method to detect MRC cells. However, the application of this approach for detecting disseminated epithelial cancer cells is difficult because of tumor cell heterogeneity. Several groups have developed RT-PCR assays that screen for epithelial-specific or tumor-associated mRNA species in samples from mesenchymal organs such as bone marrow, peripheral blood, and lymph nodes.\(^7\) Promising probes include RT-PCR assays for mRNA encoding prostate-specific antigen, cytokeratins, carcinoembryonic antigen, epithelial growth factor, and possibly proteins expressed by the genes MAGE and BAGE.\(^7,9\) In patients with lymphomas or multiple myeloma, the PCR approach appears to be clinically useful because these tumor cells reveal specific genomic characteristics including certain chromosome translocations or monoclonal expansion of a particular immunoglobulin rearrangement. This allows the routine detection of approximately 1 tumor cell in 10\(^6\) normal cells and, on some occasions, 1 in 10\(^7\) normal cells.

### Incidence of Tumor Cell Contamination in PBSC Products and Marrow Harvests: Choice of Graft

The choice between the use of harvested marrow or PBSC as the graft may still be an issue in HSCT. Currently, PBSC products are being used in a large proportion of the HSCT patients. This form of transplant has the advantage of a rapid hematopoietic recovery after marrow- ablative therapy. In addition, considerable data are now available that show a reduced risk of tumor cell contamination in the PBSC product compared with the marrow.

Studies in breast cancer have shown that approximately 3% to 22% of patients with stage IV breast cancer will have contamination of the PBSC product.\(^1,4,10,14,15\) This compares to a frequency of 36% to 82% in harvested marrow (Table 1).\(^1,8,11\) For patients with high-risk stage II/III disease, tumor contamination ranges from 4% to 16% in the PBSC vs 36% to 55% in the marrow. In addition, the amount of tumor contamination in the marrow is significantly higher than in PBSC.\(^4\) Ross et al found that the geometric mean concentration of tumor cells in PBSC specimens was 0.8/10\(^5\) mononuclear cells (range: 0.33-2.0/10\(^5\)) compared with 22.9/10\(^5\) mononuclear cells in marrow (range: 1-3000/10\(^5\), P<0.0001).

<table>
<thead>
<tr>
<th>Table 1. – The Incidence of Breast Cancer Cells in Harvested Marrow and PBSC Collections</th>
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<tbody>
<tr>
<td><strong>Graft</strong></td>
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</tr>
<tr>
<td>Marrow</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>PBSC</td>
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For patients with high-risk stage II/III disease, tumor contamination ranges from 4% to 16% in the PBSC vs 36% to 55% in the marrow. In addition, the amount of tumor contamination in the marrow is significantly higher than in PBSC.\(^4\)
The incidence of tumor contamination in myeloma and lymphoma patients appears to be greater than that seen in breast cancer. Both the level and degree of contamination of the marrow and the PBSC products are much greater. The contamination of the PBSC product can range from 20% to 100%, depending on the study. The marrow in the majority of patients contains occult cells. The clinical significance of contamination of PBSC is not clear at this time (see below).

Like breast cancer, some data suggest that the tumor burden in the marrow is greater than that in the PBSC. Vescio and colleagues found that tumor cells contaminating marrow harvest had a median concentration of 0.74% compared with 0.0024% in the PBSC. The median ratio of infused tumor cells was 14:1 when comparing marrow to PBSC. Conflicting results exist for patients with non-Hodgkin’s lymphoma. Leonard et al have shown that the number of lymphoma cells in the marrow was 0.48 logs greater than in the PBSC (P=0.0001). In some studies, PBSC has a lower tumor burden, while in other studies, there appears to be no difference between marrow and PBSC.

Timing of Pheresis and Incidence of Tumor Contamination

Information regarding the optimal amount of chemotherapy given prior to performing pheresis is increasing. Two studies in breast cancer show a decreased incidence of tumor contamination when pheresis is performed after 2 or 5 cycles of chemotherapy. In one study, the incidence of tumor contamination in 172 samples analyzed was 23% after one cycle of therapy, 5% after the second cycle, and 7% after the third cycle of induction therapy. This study clearly demonstrates that patients with stage IV breast cancer should not be mobilized after the first cycle of induction therapy. In another study, Passos-Coelho and colleagues demonstrated a marked decrease in tumor contamination of the PBSC product in stage IV patients after 5 cycles of induction chemotherapy.

There are no clear-cut studies in lymphoma or myeloma patients regarding the timing of pheresis. It is known that the majority of patients have PCR-positive PBSC products. It is also clear that patients at diagnosis have a high tumor burden in the marrow. However, it is not known what happens to the incidence and amount of tumor cells in the circulation after receiving induction therapy.

These breast cancer studies demonstrate that a cleaner product is obtained following in vivo tumor eradication. However, it is well known that the number of CD34+ cells mobilized into the PBSC product is reduced by increasing the duration of chemotherapy. Additional investigative studies are needed to help to determine the guidelines regarding when and how to mobilize high-risk patients in order to result in the lowest incidence of tumor contamination of PBSC products.

Do Cytokines Mobilize Tumor Cells?

Little is known about the effect of cytokines on the mobilization of tumor cells. Brugger et al demonstrated an association between the use of G-CSF and the presence of tumor cells in the circulation after the first cycle of chemotherapy in patients with advanced disease. These data have resulted in a heightened awareness of the effects of cytokine drugs on mobilization of tumor cells.

In one study, ICC analysis was performed on PBSC products taken prior to high-dose therapy followed by HSCT from 775 patients with stage II or IV breast cancer. The incidence of tumor contamination in PBSC products was greater for stage IV patients (97 of 470 patients; 21.3%) when compared to patients with stage II disease (30 of 206 patients; 14.6%; P=0.04). This difference disappeared when stage IV patients were mobilized with chemo/cytokine therapy (38 of 240 patients, 15.8%).

The type of mobilization regimen chosen affects the incidence of tumor contamination found in PBSC products. To date, no difference has been found in the incidence of tumor contamination of PBSC and the type of cytokine used. Further studies should be conducted to determine if the type of chemotherapy used is associated with the amount of tumor contamination.

Marrow Disease and Tumor Contamination of PBSC Products

Mounting evidence suggests that circulating neoplastic cells are almost always present when marrow disease is overt and that graft contamination may be present even when the marrow is tumor-free. The presence of marrow disease is associated with an extremely high rate of positive PBSC samples in stage IV breast cancer. Patients with ICC-positive marrow had 21 of 60 (35%) PBSC products contaminated with breast cancer cells compared with 31 of 168 (18.4%) for those patients with ICC-negative marrow (P=0.009). A few studies in myeloma and lymphoma patients show a correlation between the presence of marrow disease and tumor contamination of PBSC product. However, it must be remembered that, like patients with breast cancer, contamination of PBSC can occur when the marrow is PCR-negative for disease. In fact, the incidence of tumor cells in the PBSC product when the marrow is negative is greater for patients with lymphoma or myeloma than for patients with breast cancer.

Although for breast cancer patients, the marrow disease appears to be associated with the presence of tumor cells in the PBSC, mobilization regimen does have an impact in the ICC marrow-negative group. For patients whose marrow was ICC negative, mobilization with chemo/cytokine therapy produced the lowest incidence of contamination in the PBSC product (8 of 86; 9.3%). This was significantly better than those who were mobilized with cytokines alone (22 of 63; 34.9%, P=0.0001). This difference is not seen in the patients with ICC-positive marrow.

This study shows that the use of cytokines only for mobilization of PBSC may be associated with a greater risk of tumor contamination. However, a number of other factors may play a role in the incidence of tumor contamination of the PBSC product. Further prospective studies are needed.
Number of Phereses and Tumor Cell Contamination

Studies are now available to show that increasing the number of phereses dramatically increases the number of patients with tumor contamination of the PBSC product (Table 2). Indeed, the two studies published indicate that the number of phereses may be the best predictor of tumor cells in the PBSC. These studies demonstrate that the more phereses analyzed per patient, the greater the chance of finding tumor contamination of PBSC products. The incidence of positive PBSC ranges from 5.4% for a single pheresis to 30.7% when three phereses are performed. Using a statistical model, the dramatic increase in tumor contamination of PBSC with three or more phereses is not related to the number of testing events. Despite these data, it is not known if this increase in tumor contamination truly represents an increase in incidence, if it is caused by simply performing more ICC testing per patient, or if it is solely reflective of a patient with high tumor burden or poor CD34+ mobilization capabilities. Prospective and retrospective studies are ongoing to determine the significance of these initial findings.

<table>
<thead>
<tr>
<th>Number of Phereses</th>
<th>Number of Patients PBSC-</th>
<th>Number of Patients PBSC+</th>
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<tbody>
<tr>
<td>1</td>
<td>138</td>
<td>8 (5.4%)</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>15 (15.1%)</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>27 (30.7%)</td>
</tr>
<tr>
<td>≥4</td>
<td>70</td>
<td>48 (40.7%)</td>
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</tbody>
</table>

Clinical Significance

Two questions involve the use of MRC testing of the graft: (1) what is the predictive value of finding occult tumor cells in harvested marrow or PBSC, and (2) does the infusion of tumor cells in the graft into the HSCT patient directly result in relapse of disease?

It is now clear that the prognostic power of MRC testing is very good. A number of studies demonstrate that the presence of MRC in harvested marrow is predictive of a poor clinical outcome for patients with breast cancer, lymphoma, and myeloma. In addition, some data show that the presence of occult marrow disease in an aspirate around the time of HSCT is also highly predictive of a poor clinical outcome. The relationship between the presence of tumor cells in the PBSC and clinical outcome post-HSCT therapy is less clear, particularly for patients with lymphoma and myeloma. However, some studies in breast cancer suggest that the presence of tumor cells in the PBSC is related to a poor clinical outcome.

For breast cancer, Vredenburg et al and Fields et al have shown that the presence of tumor cells in harvested marrow is predictive for outcome in patients with stage II (>10 positive lymph nodes) or stage IV disease. Moss et al and Moreb et al have shown that the presence of occult tumor cells in marrow aspirates obtained around the time of HSCT is highly predictive of relapse post-HSCT therapy (Table 3). Gribben et al have shown that the presence of lymphoma cells following chemotherapy purging of harvested marrow correlates with a poor clinical outcome. Similarly, Sharp and colleagues have shown that the presence of culture positive lymphoma cells in harvested marrow correlates strongly (57% vs 17% in complete responders) with a poor post-HSCT clinical outcome. Hardingham et al have shown that the persistence of marrow PCR positivity in patients with lymphoma portends a poor prognosis.

<table>
<thead>
<tr>
<th>Stage of Disease</th>
<th>Marrow-Positive Pts</th>
<th>Marrow-Negative Pts</th>
<th>Relapse Rate: Marrow-Positive Pts</th>
<th>Relapse Rate: Marrow-Negative Pts</th>
<th>Author</th>
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</thead>
<tbody>
<tr>
<td>II</td>
<td>30</td>
<td>53</td>
<td>63%</td>
<td>40%; p=0.04</td>
<td>Vredenburg et al</td>
</tr>
<tr>
<td>II-III</td>
<td>24</td>
<td>120</td>
<td>67%</td>
<td>18%; p&lt;0.0001</td>
<td>Umiel et al</td>
</tr>
<tr>
<td>IV</td>
<td>41</td>
<td>9</td>
<td>94%</td>
<td>14%; p=0.0002</td>
<td>Fields et al</td>
</tr>
<tr>
<td>IV</td>
<td>38</td>
<td>195</td>
<td>NS</td>
<td>p=0.01</td>
<td>Moss et al</td>
</tr>
</tbody>
</table>

NS = not stated

Pecora et al have shown that patients who are mobilized with chemotherapy and cytokines and have tumor-contaminated PBSC product have a poor prognosis. It also appears that the clonogenic growth of circulating breast cancer cells may strongly correlate with clinical outcome (Table 4). For patients with lymphoma, one study to date demonstrates that tumor contamination of PBSC products portends a poor prognosis. It should be noted that not all patients who receive graft products known to contain tumor cells will relapse following high-dose therapy. Consequently, not all reinfused tumor cells cause relapse of disease.

<table>
<thead>
<tr>
<th>Tumor Colonies</th>
<th>No Colonies</th>
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<tbody>
<tr>
<td>Patients</td>
<td>38</td>
</tr>
<tr>
<td>Relapses</td>
<td>37</td>
</tr>
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Disease-Free Survival* | 10% | 35%

* Clinical outcome was then determined using the Kaplan-Meier survival curve analysis
Although currently there is no direct evidence that infusion of tumor cells is solely responsible for relapse of disease, studies have shown that tumor-contaminated grafts may contribute to relapse for patients with leukemia or neuroblastoma. In these studies, gene-transfected tumor cells from reinfused harvested marrow were found in patients who relapsed posttransplant. These tumor cells were identified in old sites of disease as well as in new sites. However, for patients with stage IV disease, relapse after autologous bone marrow transplantation is most likely multifactorial. Failure can be due to resistant disease, an inadequate conditioning regimen, a dysfunctional immune system, or tumor contamination in the reinfused graft. The data presented above showing the strong correlation between the presence of clonogenic breast cancer cells in PBSC product and poor clinical outcome suggest that infusion of tumor cells may contribute to relapse. Unfortunately, definitive studies to determine the role that reinfusion of tumor cells plays in the HSCT patient may be impossible to conduct.

**Ex Vivo Purging/Expansion of Stem Cell Products**

To purge or not to purge -- that is the question. Based on discussions with many colleagues, it appears that this issue borders on religion. Either you believe or you don't, with a few agnostics thrown into the group. There is no right or wrong approach to purging. The arguments in favor of purging the graft include the following: (1) the reinfusion of tumor cells contributes to relapse, (2) any therapy that reduces the tumor burden will promote better long-term survival, (3) high-risk patients with aggressive tumor cells in the graft (eg, clonogenic cells) require a unique approach, (4) purging does not affect engraftment and is proven to remove tumor cells, and (5) my competitor is offering this service and I don't want to lose business. The arguments against purging include the following: (1) there is no direct evidence that it causes relapse, (2) the patient's immune system will eradicate any few reinfused tumor cells, (3) patients with aggressive cancer and tumor cells in the graft will relapse regardless of therapy, (4) the use of effective post-HSCT therapy will obviate the need to purge the graft, and (5) the procedure is costly and I might lose third-party payer contracts.

A key issue for purging is how to measure the efficacy of the purge. Quantitative assays will determine log depletion. However, it is important to note that in CD34 selection, the majority of the product is infused into the patient and the material available for MRC testing may be limited, thus reducing the sensitivity of the assay. For instance, large numbers of cells in the preslected product, there is a sensitivity of 1/1,000,000. However, the number of CD34-selected product available for ICC testing is usually 1,000,000 cells or fewer. Thus, the sensitivity of the MRC test on the CD34 product may be 1 log lower or 1/100,000. Therefore, quantitation of tumor cell purging could be off by 1 log if one assumes the MRC test on the CD34 product is 1/1,000,000 if negative. In addition, it may be important to include functional assays (eg, clonogenic capacity) in conjunction with traditional MRC detection assays in order to measure the true efficacy of ex vivo purging techniques. This measures log reduction of tumor cells and reduction or eradication of clonogenic cells.

Since marrow contamination has been demonstrated in harvested marrow, purging methods have been devised for breast carcinoma, lymphoma, or myeloma. Several preclinical and a few clinical studies in breast cancer, lymphoma, or myeloma have demonstrated the feasibility of ex vivo purging. In one of these studies, hydroxypropylcyclodextrin was used to purge marrow specimens from advanced-stage breast cancer patients. In that study, even though tumor cells were detected by ICC analysis following purging, they did not grow in a tumor cell clonogenic assay. Unfortunately, the use of chemotherapeutic agents may cause a prolonged time to engraftment and currently are not widely applied to HSCT.

CD34 selection is the most widely applied purging method available and in use today. This therapy isolates stem cells from the graft and thereby promotes more effective engraftment. It effectively and passively removes tumor cells but does not adversely affect engraftment (provided that adequate numbers of CD34+ cells are infused into the patient). Using CD34 selection, tumor cell removal has been documented at up to 4 logs for patients with breast cancer, lymphoma, or multiple myeloma. However, patients with a high tumor burden in the graft can have residual neoplastic cells in the CD34 product. To improve tumor cell purging, techniques that rely on the active removal of tumor cells have been developed. These methods employ the use of antitumor monoclonal antibodies either with immunomagnetic beads or particles or with avidin-biotin columns. With these methods, an additional 1 to 2 logs of tumor cell removal may be obtained.

Another interesting concept in the transplant community is the use of growth factors to promote ex vivo expansion of hematopoietic cells. Two studies have shown that tumor contamination of the ex vivo expanded product can occur. However, although one study shows that tumor cells markedly decrease after ex vivo expansion (tumor cell purging), it is unclear whether these tumor cells maintain their capacity for growth in vivo.

In conclusion, although indirect evidence exists, it is not clear if purging of the PBSC product will result in an increase in disease-free survival. The investigator must determine the individual clinical need for this type of therapy.

**Functional/Biologic Assays for MRC**

The goal of MRC testing is to provide prognostic data to assist the clinician in making more effective therapeutic decisions for the oncology patient. Assays such as ICC and PCR may provide some prognostic information. However, supplemental testing that may further improve the prognostic value of MRC testing is needed. Qualitative tests on micrometastatic tumor cells may provide this additional information. These types of tests include the determination of the viability and growth potential of these cells, the expression of significant biologic markers (eg, HER-2/neu, multidrug resistance, etc), and/or the assessment of the invasive capacity.

The most advanced of these methods is the use of cell culture assays to determine the viability and growth capacity of micrometastatic cells. Several investigators have used such methods to grow tumor colonies from patient marrow in agar or in liquid culture systems. The liquid culture system is derived from traditional cell culture techniques that are known to facilitate tumor growth in vitro. The assay is based on the principle that tumor cells can be maintained in an in vitro environment and that tumor cells can be detected by ICC analysis following purging, they did not grow in a tumor cell clonogenic assay. Unfortunately, the use of chemotherapeutic agents may cause a prolonged time to engraftment and currently are not widely applied to HSCT.

These clonogenic methods have been shown to be more effective than routine pathologic analysis at identifying tumor contamination of bone marrow specimens from patients with breast carcinoma, lymphoma, and neuroblastoma. However, the sensitivity of these assays is difficult to determine. This is due in part to the small number of tumor cells capable of producing colonies (plating efficiency), even if highly malignant cells are used (eg, neoplastic cell lines). The disadvantages of using cell culture assays include the risk of culture contamination and the substantial time interval (often weeks) between processing the specimen and obtaining results. However, culture-based tumor detection assays are the only methods that determine the viability of occult tumor cells and measure their in vitro growth potential. This type of assay is highly predictive of relapse in HSCT patients with breast cancer or lymphoma.

Preliminary work has been done to determine the expression of gene products in micrometastatic cells. A dual-labeling ICC approach has been developed that can identify the tumor cell and determine expression of epidermal growth factor receptor, prostate-specific antigen, etc, by these cells. Further studies are in progress to determine the clinical significance of these preliminary findings.
Conclusions

MRC testing is being used with increasing frequency in the field of HSCT for patients with breast cancer, lymphoma, or multiple myeloma. Quantitative testing is being used clinically to help in determining who is responding to induction therapy, who is at high risk for relapse post-HSCT therapy (and thus eligible for alternate, novel therapy or additional post-HSCT therapy), and who has tumor-involved graft. A number of HSCT physicians are using this information to construct new clinical protocols aimed at improving long-term disease-free survival. They are also constructing novel mobilization regimens to reduce the risk of tumor contamination of the PBSC product. Newer, more qualitative assays may provide additional prognostic information to further guide HSCT physicians in clinical decision making.

References


