

and RT in FA patients is feasible and may be successful. Even if this double procedure might imply some adjunctive risks of late tumors, it has ameliorated the duration and the quality of life of this patient.

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To the editor:

Cytomegalovirus infections in cancer patients receiving granulocyte transfusions

Because of the high risk of transfusion-transmitted cytomegalovirus (CMV) infection associated with the use of granulocyte concentrates, it is common blood bank practice to provide only CMV-seronegative granulocytes to patients who are CMV seronegative.¹ Recently, Narvios et al challenged this practice.² In their case series of 100 cancer patients who received CMV unscreened granulocyte transfusions, they report that only 4% developed CMV infection and that all 4 patients were CMV seropositive prior to the granulocyte transfusions. Thus, they suggested that screening granulocyte donors for the presence of CMV infection is not needed.

Several problems with this conclusion are evident. The primary CMV-related concern with unscreened granulocyte transfusions is for transfusion-transmitted CMV infection (TT-CMV) in the CMV seronegative recipient, yet no details regarding the CMV serostatus of the granulocyte recipients were presented. The prevalence of CMV seropositivity in their cancer patients is likely to be even higher than that of their donor pool (70%-80%), as cancer patients are commonly multiply transfused. Thus, CMV-seronegative granulocyte recipients likely represent a minority (< 20%) of patients in the cohort. Second, it is unclear whether CMV infection or CMV disease (such as pneumonitis) is being reported. There is also no information provided whether prospective monitoring for primary CMV infection was performed in this cohort of mostly chemotherapy recipients. Thus, the true incidence of CMV infection cannot be obtained from these figures. What is at issue in this context is the true rate of CMV infection associated with granulocyte transfusions. Thus an analysis that focused upon CMV-negative recipients and included prospective monitoring for CMV infection would have been more informative. Fortunately, such studies have been performed in the setting of stem cell transplantation (SCT),³⁻⁶ and they demonstrated a very high rate of primary CMV infection when granulocytes from CMV-seropositive donors are administered to CMV-seronegative recipients. These studies are the basis for present blood center recommendations.¹

The authors also failed to distinguish important differences in patient populations with regard to risks associated with CMV infection; the risk

for progression from CMV infection to CMV disease is in parallel with the degree of immunosuppression. Certainly, SC transplant recipients are at the highest risk for CMV disease, but recently published data from the authors' own institution suggest that CMV disease is "an emerging problem" in adults with leukemia receiving conventional chemotherapy as well.^{7(p539)} In that report, immunosuppressive regimens containing fludarabine, steroids, cyclophosphamide, or, interestingly, granulocyte transfusions from CMV-unscreened donors were implicated.⁷ Current guidelines for the use of "CMV-safe" blood products include the use of either CMV-seronegative or *leukocyte-reduced* cellular blood products for CMV-seronegative patients at high risk for CMV-related morbidity and mortality. As such, the use of granulocyte transfusions from CMV-positive donors (products that are obviously leukocyte-rich and, thus, more likely to transmit virus) for CMV-negative SC transplant recipients is untenable. Given the poor outcome associated with CMV seropositivity in patients who undergo SCT,⁸ those who are candidates for SCT should also receive CMV-negative products. "CMV-safe" components should be strongly considered for CMV-seronegative patients with significant chemotherapy-induced T-cell immunodeficiency (such as those receiving fludarabine or other T-cell suppressing therapies) given the data presented above.

The argument that the requirement for CMV-seronegative donors diminishes the potential donor pool has also been raised.² In our experience of 76 recipients of granulocytes from related or unrelated donors,⁹ the CMV-seronegative rate was approximately 40%. We did not encounter problems in recruiting CMV-seronegative donors for these patients. While it is true that communities with a high CMV-seroprevalence rate have a smaller seronegative donor pool, it should also be pointed out that the demand for such products may be less.

Finally, the authors indicate that granulocyte colony-stimulating factor (G-CSF)-stimulated granulocyte transfusions are "clearly ... effective."^{1(p391)} But this point remains controversial. In that uncontrolled case series, 47% of patients demonstrated a favorable response to granulocyte transfusions, though response was dependent on underlying infection type.¹⁰ The interpretation of uncontrolled series is difficult,

since a significant proportion of these infections would be expected to respond to antimicrobial therapy alone. In a case-control study of severely neutropenic SC transplant recipients with invasive infections who received granulocyte transfusions, we recently showed that G-CSF-mobilized granulocyte transfusions were not clearly associated with improved outcomes.⁹ In that study, patients were carefully matched according to infection type, underlying conditions, and transplantation status. Only a randomized controlled trial can definitively answer this question; planning for such a study is currently under way.

We conclude that the effectiveness of therapeutic granulocyte transfusions requires further study. With regard to CMV matching, we believe that the data provided by Narvios et al are not sufficient to establish policy. Due to the significant risks associated with TT-CMV in some CMV-seronegative patient populations, it seems prudent to transfuse only CMV-seronegative granulocytes if possible. If CMV-seronegative granulocytes are not available, we suggest that high-risk recipients (ie, SC transplant recipients) be monitored for CMV by antigenemia or polymerase chain reaction (PCR) and treated preemptively if infection is documented.

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To the editor:

Expression of survival receptors in Hodgkin disease cell lines

A unique feature of Hodgkin disease (HD) is the small number of malignant Hodgkin and Reed-Sternberg (HRS) cells in diseased tissue. Growth of HD-involved lymph nodes is mostly the result of an infiltration of benign T cells. Because of their scarcity, HRS cells are not easily isolated from the vast number of surrounding T cells, and this explains why functional data from single HRS cells are difficult to obtain.

HRS cells, which originate from germinal center B cells, frequently contain crippling somatic mutations within rearranged immunoglobulin heavy chain genes.¹ Because such crippling mutations trigger apoptosis in germinal center B cells, their detection in HRS tumor cells has supported the view that the lack of surface immunoglobulin-mediated protection from apoptosis must be compensated through expression of surrogate survival factors. Since receptor activator of nuclear factor κ B (RANK) promotes survival of dendritic cells, detection of RANK in HRS cells could help explain their ability to escape apoptosis.

In a recent report, Fiumara et al examined the expression of RANK in 4 HD-derived cell lines,² assuming that these cell lines retained the molecular signature of the founder HRS tumor cells from which the lines originated. RANK expression was clearly demonstrated in 2 HD cell lines (HDLM-2 and L-428 cells). The other 2 HD cell lines (HD-MYZ and KM-H2) did not express significant amounts of RANK. Among all HD cell lines tested, RANK ligand (RANKL)-mediated activation of nuclear factor κ B (NF κ B) was most pronounced in HD-MYZ cells, and addition of exogenous RANKL to these cells strongly induced interleukin-8 mRNA. This result is not easily explained because HD-MYZ cells fail to synthesize detectable amounts of RANK, the receptor that transduces RANKL-mediated signals. Equally puzzling is a lack of NF κ B activation in RANKL-stimulated L428 cells, which, contrary to HD-MYZ cells, express high levels of RANK. Finally, the high-level expression of RANKL in all 4 HD cell lines remains largely unexplained.

Fiumara et al further examined whether exogenous RANKL would affect the proliferation of HD-MYZ, HDLM-2, L428, and KM-H2 cells, thereby testing a possible role for RANK in regulating cell growth of HD tumor lines. The authors found that proliferation rates remained completely unaffected by the addition of RANKL. This result casts further doubt on the significance of RANK expression in HD cell lines.

The problems associated with the use of tumor cell lines as a model for HD are demonstrated by the expression of the interleukin-3 receptor (IL-3R). IL-3R rescues cells from apoptosis³ and, like RANK, is expressed in some but not all HD cell lines. As shown in Table 1, whether HD cell lines express IL-3R depends, to

Table 1. Relative IL-3R surface expression in HD cell lines

Cell line	Origin	EBV status	IL-3R-associated surface fluorescence
DAUDI	B	+	0.3
RAJI	B	+	0.6
JJAN	T	-	0.0
SUPT1	T	-	0.0
KM-H2	HD	-	0.0
HO	HD	-	0.0
L591	HD	+	6.5
L1236	HD	-	10.5
HDLM-2	HD	-	60.6
L428	HD	-	100.0

HD cell lines (KM-H2, HO, L591, L1236, HDLM-2, L428) were labeled with a murine monoclonal antibody directed against human IL-3R (7G3, Cambridge Bioscience, Cambridge, United Kingdom) and cell-bound IgG visualized with phycoerythrin (PE)-conjugated antimouse IgG (Dako, Glostrup, Denmark). Relative surface fluorescence was determined by flow cytometry (FACSCalibur, Becton Dickinson, Franklin Lakes, NJ). Human B (DAUDI, RAJI) and T (JJAN, SUPT1) lymphocyte cell lines were used as controls. Not represented among HD cell lines are HD tumors containing Epstein-Barr virus (EBV)-positive HRS cells, which account for approximately half of all HD cases.