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Does Chemotherapy Modify the Immune Surveillance of Hematological Malignancies?

A John Barrett[1] and **Bipin N Savani**[2]

[1]Hematology Branch, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA

[2]Veterans Affairs Medical Center and Vanderbilt University Transplant program, Nashville, TN, USA

Abstract

Malignant diseases induce immune responses against them which have variable success in controlling progression of disease. A variety of congenital and acquired disorders provide evidence in support of T cell or NK cell immune surveillance mechanisms in human hematological malignancies. Furthermore clinical experience with stem cell transplantation underlines the potential for both T and NK cell mediated anti-leukemia effects. Animal models of tumor surveillance and viral driven lymphoproliferative diseases in man emphasize the dynamic nature of the equilibrium between tumors and the immune system which can lead to tumor escape in individuals with normal immune function. In hematological malignancies the implication of a dynamic immune surveillance model is that chemotherapy may disrupt potentially competent immune surveillance mechanisms leading to disease recurrence following successful tumor bulk reduction by chemotherapy. This possibility deserves further investigation with a view to developing strategies to boost immune function following chemotherapy so as to combine the beneficial effect of chemotherapy with an immune response capable of sustaining remissions.

Keywords

Lymphocyte recovery; immune surveillance; leukemia; lymphoma

Introduction

The concept that the immune system can protect the host against cancer was proposed by Ehrlich in 1909 and again, in modern terms, by Thomas and Burnet in the 1960s [1–3] who suggested that lymphocytes continually identify and eliminate newly arising cancer cells through a process they called “immune surveillance” Immunodeficient mice were indeed found to be at greater risk for spontaneous tumor development [4] and in man, both congenital and acquired T cell immunodeficiency predispose to malignancies, often driven by DNA viral proliferation uncontrolled by the immune system.[4;5] Finally, evidence for immune

Corresponding Author: John Barrett, M.D., Stem Cell Allogeneic Transplantation Section, Hematology Branch, NHLBI, NIH, Building 10, Hatfield CRC, Room 3-5330, 10 Center Drive MSC 1202, Bethesda, Maryland 20892-1202, Tel: 301-402-4170, Fax: 301-496-8396, barrettj@nhlbi.nih.gov.

surveillance in cancers comes from numerous observations correlating lymphocyte tumor infiltration with a more favorable prognosis.[6–8]

More recently the concept of immune surveillance has broadened with the realization that the interaction of the immune system with the malignancy [9] is a ongoing dynamic process where the immune system is modified by the tumor and the tumor in turn is modified by the immune system (immune editing).[10] The immune control of malignancy is thus best understood as an equilibrium, which when perturbed, may adversely cause tumor escape or favorably re-establish tumor control and eventual elimination.[4] A recent study of carcinogen-induced spontaneous tumors in mice supports this model as the most likely for cancers developing in individuals with normal immune competence.[11] When carcinogens were given to a large population of mice, the subsequent evolution of the cancer was variable. About 40% of mice did not develop overt cancer, but on further investigation were found to have occult tumors which grew poorly in the presence of a competent immune system. In some mice, tumor cells in equilibrium underwent clonal selection and then escaped immune control to develop into lethal cancers, however many animals remained tumor-progression free unless they received immunosuppression with cyclosporine. Finally interferon gamma treatment re-established immune control over the tumor. This dynamic model of immune surveillance raises practical questions about standard treatment approaches to malignant disease and to hematological malignancies in particular: is it possible that the tumor bulk reduction or remission induction of leukemia achieved by chemotherapy and radiation therapy might lose some of its benefit by compromising immune surveillance causing subsequent tumor escape? Here we review immune surveillance as it occurs in leukemia and lymphoma, explore the concept of equilibrium as reflected in the treatment of hematological malignancies and discuss the implications for improving treatment outcomes by combining chemotherapy with immunotherapeutic strategies. We will discuss conditions which lead to tumor escape in individuals who originally have competent immune systems. Not discussed further here, but cited in support of the control of malignancy by T cells or natural killer (NK) cells are the congenital immune deficiency syndromes where impaired immunity leads to hematologic malignancies.[5]

Immune surveillance in hematological malignancies

It is likely that individual malignancies have specific interactions with the immune system and further refinement of the concept of immune surveillance demands descriptions of immune interactions with specific tumor types. In this regard hematopoietic malignancies have unique features distinguishing them immunologically from non-hematopoietic cancers; NK cells specifically target normal and malignant cells of the hematopoietic lineage [12–14], and both myeloid and B cell lineages include professional antigen-presenting cells, favoring the recognition of myeloid and B cell malignancies by T lymphocytes. Clinical experience with allogeneic stem cell transplantation provides ample evidence for the existence of strong immune responses against leukemias and lymphomas mediated by alloreacting T cells and NK cells through graft-versus-leukemia (GVL) effects. While GVL is predominantly driven by allo-responses to non-self antigens not present in the stem cell donor, it can provide a

realistic model of how T cells and NK cells can successfully engage and destroy hematological malignancies.

Immune surveillance in specific hematological disease states

EBV lymphoproliferative disease

Epstein-Barr virus (EBV) B cell lymphoproliferative disease is one of the best characterized interactions between the immune system and a human hematologic malignancy. The interaction between the immune system and the B lymphoproliferative process is driven by viral antigens and may be considered a special case. However, it is instructive to observe how in normal health, controlled by a large repertoire of memory T lymphocytes, lifelong suppression of a viral driven B cell proliferation is achieved. Suppression of T cell reactivity to EBV in HIV infection, after solid organ or stem cell transplantation and rarely after chemotherapy or anti T lymphocyte antibody-mediated immunosuppression results in an outgrowth of an EBV-driven B cell tumor.[15] These rapidly proliferating bulky tumors can regress after the withdrawal of immunosuppression, if that was the predisposing factor for lymphoproliferation, or more dramatically (with an accompanying cytokine storm) by the adoptive transfer of EBV-specific T cells.[16] The tumor may undergo further adaptive mutations which escape T cell control and downregulation of the major EBV antigen (Epstein-Barr nuclear antigen) EBNA results in the outgrowth of a lymphoma uncontrolled by T lymphocytes.[17] The EBV lymphoproliferative disease model has implications for immune surveillance in other hematological malignancies. First, the fact that a large memory T cell pool is needed to maintain a viral-driven proliferative process indicates that even strongly antigenic malignancies may require a large immune repertoire to control them. Second the inverse relationship between immune competence and B cell proliferation clearly defines the limits to effective immune control caused by immunosuppressive treatments and supports the possibility that T cell mediated immune responses to other hematological malignancies are significantly suppressed by routine chemotherapy treatments.

Infiltrating lymphocytes in lymphomas

The observation that lymphocyte-rich Hodgkin's disease [18] have a less aggressive or more favorable outcome than T cell poor pathologies conforms to a large body of data in non-hematological malignancies indicating at least a partial relationship between tumor infiltrating lymphocytes and tumor growth control. However T cell rich non-Hodgkins lymphomas do not appear to have a more favorable outcome [19] Recent evidence in solid tumors that the proportion of regulatory T cells to effector T cells determines prognosis has not yet been evaluated in lymphomas.[20;21]

Myelosuppressive T cells in myelodysplastic syndromes (MDS)

There is evidence that T lymphocytes contribute to the marrow failure of some patients with MDS. About 30% of patients with early stages of MDS will respond to immunosuppression with an increase in blood counts and a loss on transfusion dependence.[22;23] It is hypothesized that the patient's CD8+ T cells recognize antigens expressed on MDS stem cells resulting in apoptosis and bystander suppression of residual normal stem cells through production of cytokines such as TNF-α and IFN-γ.[24] Such T cell suppression of a malignant

clone, while causing complications from poor marrow function could nevertheless represent a functional form of immune regulation of a pre-leukemic stem cell. However long-term follow-up has not revealed an increased rate of leukemic transformation in patients treated with antithymocyte globulin (ATG) immunosuppression. In fact ATG responders who lost transfusion dependence almost never progressed to AML in comparison with similar patients (under the age of 60 years with IPSS Int-1) who did not receive immunosuppressive treatment.[23] Thus, while there is evidence for a specific T cell mediated control over MDS in some patients, ATG used to reverse the T cell mediated cytopenia did not result in tumor escape.[25] We have therefore to conclude that in MDS the T cell regulation of dysplastic hematopoiesis is sometimes harmful, and of no significance in preventing leukemic progression.

Tumor specific T cells in leukemia

Leukemia cells present a diversity of antigens which can elicit leukemia-specific T cell responses. They include well characterized tumor-specific antigens such as Wilms tumor 1 (WT1) H-tert and PRAME, fusion proteins products of chromosomal translocation such as BCR-ABL in chronic myeloid leukemia, and peptides from primary granule proteins (including PR1 from proteinase 3) in myeloid leukemias.[26–30] Low frequencies of circulating CD8+ T cells recognizing peptides of, PR1 and Wilms tumor-1, have been identified in normal individuals which are increased in patients with leukemia.[29;30] Somewhat surprisingly the antigen-specific T cells to PR1, WT-1 in leukemia patients have characteristics that suggest immune competence rather than immunoediting by the malignancy: Unlike T cells from non-leukemic individuals, T cells from leukemia patients frequently recognize more than one peptide from the parent protein (epitope spreading), they retain high antigen affinity T cell responses, and occupy both central memory and effector memory compartments suggesting a persisting functional memory for leukemia antigens.[30] Thus, leukemias frequently appear to coexist with some form of immune control which was, nevertheless, inadequate to prevent the development of overt leukemia. The higher frequencies of tumor-specific T cells with similar features to those in leukemia patients which occur in patients in remission after allogeneic stem cell transplantation would suggest that the immune equilibrium can be shifted favorably by allogeneic stem cell transplantation.[29–31] It is therefore of great interest to study such leukemia-specific T cell responses to determine whether remission induction chemotherapy for acute leukemia also results in a favorable adjustment of the immune-leukemia equilibrium, and whether the attainment of a favorable equilibrium results in sustained remission.

Immune surveillance and treatment of hematological malignancies

GVL in autologous and identical twin stem cell transplants

In contrast to the potent GVL effects seen in allogeneic SCT for leukemia, evidence for immune control of leukemia following transplant from an identical twin donor is scanty. Some form of graft-versus-host reaction does occur following a syngeneic donor SCT which may represent a cytokine effect from immune dysregulation rather than an alloresponse to the recipient[29]. Large databases indicate that relapse rates for leukemia after identical twin transplants are significantly higher than in transplants from allogeneic donors. However

relapse rates in recipients of T cell depleted HLA matched sibling transplants are still higher, suggesting a modest protective effect from the (T cell replete) syngeneic transplant.[32] However, syngeneic SCT for multiple myeloma appear to have a probability of relapse no higher than that of HLA identical sibling donors.[33;34] Furthermore relapse risk in identical twin SCT is reduced significantly if the transplanted nucleated cell dose exceeds 10^8/kg, suggesting a GVL dose effect from either the donor lymphocytes or from NK cells derived from donor CD34 cells.[35] Thus the curative potential of identical twin SCT does not depend solely on the intensive conditioning regimen used to treat the leukemia, but may reflect some form of "non-allogeneic" GVL effect, reflecting the potential of a healthy immune system, not previously tolerized to the leukemia to confer protection against relapse when the disease is reduced to a minimal load by a myeloablative conditioning regimen.

In contrast to the syngeneic SCT data it is debatable whether a GVL effect can be discerned after autologous SCT. Despite the occurrence of an autologous GVHD syndrome,[36] GVL effects have not clearly been defined. However there appears to be some relationship between rapid lymphocyte recovery after stem cell transplantation and freedom from relapse, which is discussed further below.

Chronic myeloid leukemia - imatinib, interferon, and vaccines

The experience from allogeneic SCT and the efficacy of donor lymphocyte infusions would suggest that chronic myelogenous leukemia (CML) is the most susceptible of all leukemias to immune regulation. We were unable to demonstrate any overt reactivity of autologous T cells against leukemia or against the BCR-ABL fusion peptide in a series of CML patients at various stages in disease evolution,[37] but subsequently, increased frequencies of CD8+ T cells recognizing WT-1, and PR1 peptide have been identified in CML.[29;30] Recent studies show that patients with CML lose high affinity PR1 specific T cells which may coincide with loss of leukemia control. However, when leukemia was controlled by interferon, high affinity PR1 specific T cells with greater cytotoxicity against leukemia recover.[38;39] These observations are of great interest since they provide evidence of immune sculpting as well as showing that immune control can be reasserted by achieving minimal residual disease state and boosting immune function with interferon. While the introduction of tyrosine kinase inhibitors (TkI) like imatinib has dramatically altered the natural history of CML, it is now clear that CML persists at a molecular detection level despite years of treatment with TkI [40] raising the question whether the disease could be eradicated at a minimal residual disease stage by immunological means. [41] Both interferon and BCR-ABL vaccines appear promising treatments to switch the equilibrium in favor of immune regulation.[42] Whether successful immunotherapy will eradicate quiescent leukemia stem cells or simply maintain control of minimal residual disease remains to be determined.

Lymphocyte recovery after allogeneic stem cell transplantation

A growing body of data links prompt lymphocyte recovery after both HLA identical sibling and matched unrelated donor SCT with a more favorable outcome - notably less leukemic relapse, less GVHD and lower transplant related mortality, resulting in significantly higher survivals for patients who achieve more than the median total lymphocyte count around 3–6 weeks after transplant.[43–46] In a recent analysis we identified absolute NK cell count and not

CD3+ T cell count as the lymphocyte subset responsible for determining outcome.[46] The major impact was upon relapse: above the median NK cell count of 150/μl patients had <5% relapse compared with >75% for the group who had less than the median count. However the effect was observed only in the subset of patients with myeloid malignancies (MDS, CML, AML) and not lymphoid leukemias. Favorable NK recovery correlated directly with CD34 cell dose and inversely with T cell dose at transplant and was significantly more common in transplants from donors with a particular KIR haplotype (KIR 2DL2, 2DL3 and 2 DL5A).[46] Whether NK recovery was directly associated with the beneficial effect on relapse, or whether it is a surrogate marker for some other effect associated with immune recovery is not known for certain but these results suggest a possible role for NK cells in controlling residual disease after allogeneic SCT.

Lymphocyte recovery after autologous stem cell transplantation (ASCT)

ASCT is an effective treatment strategy for many hematological malignancies especially lymphomas and myeloma. Absolute lymphocyte count (ALC) recovery >500 cells/μl at day 15 (ALC-15) after ASCT is a powerful and independent prognostic factor for clinical outcome in NHL,[47;48] Hodgkins lymphoma,[49] multiple myeloma (MM),[47] and acute myelogenous leukemia,[50] The fact that the recovery of lymphocytes after ASCT influences survival, points to the clinical presence of an autologous graft-vs-tumor effect, implicating immune reconstitution after ASCT in the antitumor response.[51]

In all these studies higher early lymphocyte recovery was a strong and independent favorable prognostic factor for sustained remission after ASCT. Observations that immune recovery after ASCT in several malignancies (hematological and non-hematological) has been shown to be an independent prognostic factor for survival provide evidence for an autologous GVL effect.[51]

Lymphocyte recovery after chemotherapy

Very similar relationships between lymphocyte recovery and disease control have also been reported after chemotherapy remission induction for acute leukemia. Behl et al[52] evaluated the impact of ALC recovery after induction chemotherapy in newly diagnosed AML patients treated with standard induction and consolidation chemotherapy. ALC recovery was studied at days 15, 21, 28 after induction chemotherapy and before the first consolidation chemotherapy. Superior leukemia-free survivals (LFS) were observed at all time-points between day 15–28 when the ALC exceeded 500 cells/μl. Compared with patients with a lower lymphocyte count who had a LFS of 11 months, the median LFS was not reached in the subset with counts >500 cells/μl. Multivariate analysis demonstrated ALC≥500 cells/μl at all time points to be an independent prognostic factor for survival. Other investigators also report an association of good ALC recovery with more favorable outcome in children with acute lymphoblastic leukemia (ALL) and AML after chemotherapy. [53–55]

The mechanism underlying this association and the specific lymphocyte subset responsible for the effect is currently being investigated. Exploring whether a comparable protective effect of fast immune recovery after chemotherapy is observed after chemotherapy in other diseases such as MDS is of great importance in determining whether the relationship

between disease control and lymphocyte recovery is a general phenomenon, especially because it might be possible to enhance lymphocyte recovery with appropriate use of cytokines, or to minimize chemotherapy-induced damage to the immune system.

Conclusions: can we improve treatment outcomes by restoring immune competence after chemotherapy?

The original concept of immune surveillance of malignancy has been considerably refined since the first proposals over 50 years ago. In particular we now have a working model of the interplay between malignant cells and immune cells and some clues as to what controls the balance between the immune system and the cancer, leading either to tumor control or tumor escape. Despite a wide body of evidence of immune control of malignant tumors in animal models, the evidence for immune surveillance and control of human hematological malignancies is largely circumstantial. Clearly, the occurrence of a hematological malignancy is an indication that immune regulation has failed. However the observation that robust lymphocyte recovery after chemotherapy is associated with less relapse suggests that after chemotherapy immune regulation may be more or less favorably reset in favor of leukemia control. How chemotherapy interacts with tumor surveillance and control now becomes an important question. Chemotherapy damage to lymphocytes might be offset by the massive reduction in tumor mass achieved favoring a high effector-target ratio, and also by strong regenerative stimuli induced by lymphopenia. The impact of the homeostatic drive to recover from lymphopenia after chemotherapy was dramatically demonstrated by Dudley et al [56] who found that after fludarabine and cyclophosphamide chemotherapy, infused TIL clones proliferated and persisted in the recipient with melanoma for months, correlating with regression of metastatic disease in about half the patients. Fludarabine has emerged as an effective drug in the treatment of leukemia. It is also a powerful immunosuppressant. Could it be that some of its efficacy is due to its ability to induce profound lymphopenia leading to an exaggerated homeostatic drive and an enhanced lymphocyte recovery? Are there chemotherapy regimens that could favorably protect immune function? It would be important to study recovery of immune cells after standard chemotherapy regimens for acute leukemias and lymphomas, as well as with novel agents such as thalidomide and its derivatives to determine relationship between lymphocyte recovery and outcome in these diverse settings. Recent studies have reported that NHL patients treated with lenalidomide experienced higher response rate to lenalidomide if the patients had a higher ALC at the time of treatment. [57;58]

If the association of lymphocyte recovery and outcome after chemotherapy and SCT is validated, therapeutic options to further enhance immune anti-malignant effects and restore the balance between immune cells and leukemia become of great interest. Firstly, to improve lymphocyte function, patients could undergo an apheresis prior to chemotherapy to collect lymphocytes which could be cryopreserved and transfused in aliquots after each chemotherapy block. Second, lymphocyte growth factors such as IL-2, IL-7, IL-12 or IL-15 could be used to boost immune recovery after chemotherapy. Lastly, the period of immune recovery and lymphocyte expansion may represent a favorable time for inducing antigen-

specific T cell expansion with vaccines given early after chemotherapy during the lymphopenic phase.

It is a sobering possibility that we may have overlooked the possibility that the increasing successes achieved with chemotherapy for hematological malignancies over the last 50 years may be ultimately limited by the collateral damage caused by chemotherapy to the immune system, reducing its ability to re-establish control over residual disease. In future it may be possible to enhance the curative effect of existing regimens by developing methods to conserve or enhance the immune component of disease control.

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