T-Cell Immunodeficiency Following Cytotoxic Antineoplastic Therapy: A Review

CRYSTAL L. MACKALL
Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland, USA

Key Words. Immunodeficiency · Thymus · T cells · Immune reconstitution

ABSTRACT
Although cancer itself is immunosuppressive, cytotoxic antineoplastic therapy is the primary contributor to the clinical immunodeficiency observed in cancer patients. The immunodeficiency induced by cytotoxic antineoplastic therapy is primarily related to T-cell depletion, with CD4 depletion generally more severe than CD8 depletion. Myeloablative therapy, dose-intensive alkylating agents, purine nucleoside analogs, and corticosteroids substantially increase the risk of therapy-induced immunosuppression. Restoration of T-cell populations following cytotoxic antineoplastic therapy is a complex process. Efficient recovery of CD4⁺ T cell populations requires thymic-dependent pathways which undergo an age-dependent decline resulting in prolonged CD4⁺ T-cell depletion in adults following T-cell-depleting therapy. Total CD8⁺ T-cell numbers recover in both children and adults relatively quickly post-therapy; however, CD8⁺ subset disruptions often remain for a prolonged period. The clinical management of patients with therapy-induced T-cell depletion involves the maintenance of a high index of suspicion for opportunistic pathogens, irradiation of blood products, prophylaxis for viral infections, and reimmunization in selected clinical circumstances. Future research avenues include efforts to rapidly rebuild immunity following cytotoxic antineoplastic therapy so that immune-based therapies may be utilized immediately following cytotoxic therapy to target minimal residual neoplastic disease. The Oncologist 1999;4:370-378

INTRODUCTION
Red blood cells, leukocytes, and platelets are short-lived, postmitotic, terminally differentiated cells, which are continuously replenished throughout life via repetitive cycles of hematopoietic stem cell differentiation. As a result, when these cells are acutely depleted by cytotoxic antineoplastic therapy, complete repopulation generally occurs within 14-21 days via hematopoietic stem cell differentiation. In contrast, T cells are comprised of a heterogeneous group of short- and long-lived cells which are themselves capable of substantial mitotic expansion. Under normal circumstances, the long-lived cells, typically contained within the “naïve” subset, are quiescent, remaining in a noncycling state for months to years while awaiting encounter with cognate antigen [1, 2]. The short-lived cells, generally contained within the effector and memory subsets, undergo variable levels of cell cycling in response to antigens which are encountered throughout the lifetime of the host, resulting in ongoing modulation of their relative contribution to the overall T-cell repertoire [3]. As a result, in healthy hosts, ongoing hematopoietic stem cell differentiation plays only a minor role in the maintenance of peripheral T-cell populations. It is perhaps not surprising, therefore, that when T cells are acutely depleted in the context of cytotoxic antineoplastic therapy, restoration of the heterogeneous populations of T cells and the reestablishment of T-cell immunocompetence is a slow and frequently incomplete process.

This manuscript will review information regarding the relative capacity for various antineoplastic therapies to induce T-cell immunodeficiency and will present currently held paradigms for explaining the observed limitations in the restoration of T-cell homeostasis after acute depletion. Current approaches to the clinical management of patients who have sustained T-cell depletion as a result of antineoplastic therapy will also be reviewed.

LYMPHOCYTE DEPLETION AS A COMPLICATION OF CYTOTOXIC ANTEOPLASTIC THERAPY

The most common infectious complications associated with cytotoxic antineoplastic therapy are bacterial infections which occur in the setting of neutropenia [4]. Clearly,
however, cancer patients are also predisposed to a variety of other infections with viral, fungal, and parasitic pathogens. Unraveling the precise contribution of specific alterations in the various components of host defense (e.g., phagocytic cells, lymphocytes, humoral defense, natural killer cells, and skin/mucosal barriers) to specific infections is difficult. Nonetheless, it is clear that deficiencies in T-cell immune competence in cancer patients contribute to a susceptibility to infections with an array of pathogens as well as the development of other complications which are listed in Table 1 [5].

Interactions between cancer and the immune system are complex. It is clear that cancer patients display varying degrees of immunosuppression at the time of presentation, prior to initiation of antineoplastic therapy. This is perhaps most pronounced in patients with acute leukemia and other conditions associated with pancytopenia who may show clinical signs of immunosuppression at the time of presentation [6]. This immunosuppression is subsequently exacerbated by prolonged and intensive chemotherapy administered with or without corticosteroids [7]. In addition, patients with previously untreated Hodgkin’s disease frequently have impaired lymphocyte proliferation to a variety of antigens [8], and patients with Burkitt’s lymphoma have been reported to show variable levels of lymphocyte depletion which relate to the stage of disease [9]. Even patients with sarcoma, a disease not classically associated with immunosuppression, occasionally show reduced peripheral blood T-cell populations at the time of presentation [10]. Despite these abnormalities in T-cell populations which exist in cancer patients at the time of initial presentation, clinically significant T-cell immunodeficiency is relatively uncommon prior to initiation of cytotoxic antineoplastic therapy.

Following initiation of cytotoxic antineoplastic therapy, opportunistic infections and complications due to T-cell immunodeficiency occur in a variety of clinical settings. Clearly, this is most severe and most frequent following autologous bone marrow transplantation (BMT) where the combination of underlying disease, intensity of the preparative regimen, T-cell depletion of the marrow graft, post-transplant graft-versus-host disease (GVHD) prophylaxis, and the immunosuppressive effects of GVHD itself contribute to a high incidence of opportunistic complications [11]. Indeed, immunosuppressive complications of autologous BMT are generally less severe despite generally similar levels of T-cell depletion [12, 13], emphasizing the important role that GVHD and immunosuppressive medications used to control GVHD play in inducing autologous transplant-related immunosuppression.

More recently, as the dose intensity of antineoplastic regimens has increased, opportunistic infections have also emerged as complications of cytotoxic antineoplastic therapy outside the realm of BMT [10, 14, 15]. The agent most commonly implicated in antineoplastic-therapy-induced immunosuppression is cyclophosphamide [16], which is capable of profound immunosuppression when administered as a single-agent at high dose intensity [16, 17]. In one study conducted at the National Cancer Institute investigating single-agent dose escalation of cyclophosphamide, a dose of 3.6-4.5 gm/m² was administered in combination with GM-CSF, with sequential cycles ensuing as rapidly as possible after myeloid recovery. In this study, neutropenic bacterial infections were uncommon, but opportunistic infections arose as the dose-limiting toxicity [10]. Therefore, while myeloid growth factors allowed compression of the cycle length by abrogating myelotoxicity, the paradoxical result was an increase in regimen-related immuno-toxicity. Similarly, recent results have shown that the use of autologous peripheral blood progenitor cell infusions can ameliorate myelosuppression following high-dose or myeloablative therapy, however such infusions do not appear capable of inducing rapid recovery of T-cell populations (Mackall et al., manuscript submitted). These results illustrate the distinctions in the regenerative pathways for myeloid versus T-cell populations following cytotoxic antineoplastic therapy.

Clinically apparent immunosuppression has also been observed recently in patients enrolled on multiagent dose-intensive regimens which were administered for solid tumors and lymphoma [10]. In one study, the dose intensity of the treatment regimen was shown to have a significant influence on the incidence of Pneumocystis carinii pneumonia, independent of other factors such as disease histology and stage at presentation [18]. Quantitation of lymphocyte populations in the peripheral blood of patients treated on such dose-intensive protocols reveals significant T-cell depletion with a more profound effect on CD4+ than

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### Table 1. Complications related to T-cell depletion in recipients of cytotoxic antineoplastic therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples of Pathogens</th>
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<tbody>
<tr>
<td><strong>Infectious</strong></td>
<td>Viral: Human Herpes viruses (Herpes simplex types 1 &amp; 2, varicella-zoster virus, Epstein-Barr virus, Cytomegalovirus), Measles, Respiratory syncytial virus, Influenza, Adenovirus</td>
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<tr>
<td></td>
<td>Bacterial: Legionella pneumophila, Listeria monocytogenes, Salmonella typhimurium, Mycobacterium tuberculosis, Atypical mycobacterium</td>
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<td>Parasitic: Pneumocystis carinii, Toxoplasma gondii, Cryptosporidia spp,</td>
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<td></td>
<td>Fungal: Candida spp, Cryptococcus neoformans, Histoplasma capsulatum, Coccioides immitis</td>
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<tr>
<td><strong>Non-infectious</strong></td>
<td>Post-transfusion graft-versus-host disease</td>
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<td></td>
<td>EBV associated lymphoproliferative disorder*</td>
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*Typically observed only in the setting of T-cell-depleted, allogeneic BMT.*
on CD8+ T-cell populations, resulting in a significantly reduced CD4/CD8 ratio. While the relationship between the degree of CD4+ depletion and the incidence of opportunistic infections has not been as extensively studied in cancer as it has in HIV infection [19], there appears to be a general correlation between the degree of CD4 depletion and the risk for opportunistic infection in cancer patients, as well. For example, when comparing the relationship between CD4 counts and opportunistic infection among patients treated on three protocols in our institution which showed variable levels of CD4 depletion, the rate of opportunistic infections was 0% with a mean post-therapy CD4 count of 120 ± 38/mm^3, 33% when the mean post-therapy CD4 count was 68 ± 16 cells/mm^3, and 67% when the mean post-therapy CD4 count was 9 cells/mm^3 [10].

In addition to alkylating agents, the purine nucleoside analogs (2’-deoxycoformycin, 2-chloro-2’-deoxyadenosine and fludarabine monophosphate) are another class of agents with a predilection for lymphocyte depletion [20-23]. These agents have a remarkable capacity for depletion of both dividing and resting lymphocytes [24], thus resulting in significant clinical activity in the setting of hairy cell leukemia and indolent lymphomas [25]. Not surprisingly, however, these agents also induce profound depletion of normal lymphocyte populations, resulting in clinical complications related to opportunistic pathogens [26]. So profound are the lymphocyte-depleting effects of these agents that they are currently under investigation as the central components of new immunosuppressive preparative regimens used to allow hematopoietic stem cell engraftment in the setting of nonmyeloablative BMT.

Another clinical scenario wherein a substantial incidence of opportunistic complications occurs in the context of antineoplastic therapy involves chemotherapy regimens administered to patients with brain tumors [27, 28]. In this case, the combination of the T-cell-depleting effects of chemotherapy and the functional alterations in cell-mediated immunity due to systemic corticosteroids results in significant immunosuppression. In addition, while radiation therapy in and of itself has modest immunosuppressive effects [29], one recent report suggests that the combination of radiotherapy and paclitaxel results in severe lymphocyte depletion when administered concurrently [30]. One regimen which appears to be notable for the lack of immunosuppression is the combination of vincristine and actinomycin D as used in the treatment of Wilms’ tumor [31].

The mechanisms by which classical cytotoxic agents induce T-cell depletion have not been well studied, but the effects are quite rapid. Within one day of the institution of cyclophosphamide therapy, there are already substantially reduced numbers of CD3+ T cells in the peripheral blood which persist throughout the duration of therapy. While classical models would suggest that alkylating agents primarily induce cell death through interference with cell division, chemotherapy induces a preferential depletion of naïve (CD45RA+) CD4+ T cells [10]. This subset has been shown to cycle at a more diminished rate than memory (CD45RO+) CD4+ T cells [2], suggesting that the lymphotoxic effect of these agents may not be dependent upon cell cycling. Indeed, in vitro studies have shown that chemotheraphy agents and radiation can induce spontaneous apoptosis in lymphoid cells and clinical observations suggest that this may occur in vivo as well [32].

With regard to other lymphocyte populations, B cells also sustain profound depletion in the context of dose-intensive multiagent chemotherapy. Generally, however, this is accompanied by only modest reductions in serum IgG levels. In contrast, serum IgM and serum IgA levels undergo significantly greater depletion as a result of dose-intensive cytotoxic antineoplastic therapy (Mackall et al., manuscript submitted). Natural killer (NK) cells, in contrast, appear to be relatively resistant to cytotoxic antineoplastic therapy, raising the possibility that they serve an important second line of host defense against viral pathogens in this setting [33].

Many of the current studies in this field have focused upon changes in T-cell number, which are clearly a predominant feature of cytotoxic antineoplastic-therapy-induced immunosuppression. There is also evidence to suggest, however, that important functional alterations may occur following cytotoxic antineoplastic therapy. We have observed the preponderance of activated T cells in vivo which appear to have a heightened susceptibility to activation-induced programmed cell death when activated by mitogens in vitro [34]. Such functional alterations could significantly limit the capacity for response to antigen in vivo. Furthermore, restrictions in T-cell receptor (TCR) repertoire diversity are likely to limit immune competence in hosts who have regenerated T cells predominantly via thymic-independent peripheral expansion [35]. Finally, recent studies have suggested that monocyte populations which are contained within peripheral blood stem cell harvests, and which frequently expand in vivo following cytotoxic antineoplastic therapy, may contribute to T-cell immunosuppression by the production of suppressive factors which inhibit T-cell function [36, 37]. Therefore, functional alterations in recovering T-cell populations may also contribute to cytotoxic antineoplastic-therapy-induced immunosuppression.

In summary, the experience thus far suggests that while cancer patients have variable levels of immunosuppression at the time of presentation, the particular agents administered and the dose intensity of the antineoplastic therapy play a large role in determining the risk for opportunistic complications. While such complications are most common
in the setting of BMT, the use of immunosuppressive agents as part of dose-intensive regimens can lead to profound immunodeficiency in the non-BMT setting as well. The immunodeficiency induced by anticancer therapy appears to be primarily related to lymphocyte depletion, and perhaps most importantly to CD4 depletion wherein increased depletion is associated with a higher incidence of opportunistic complications.

**Recovery of T-Cell Populations Following T-Cell Depleting Therapy**

When absolute lymphocyte counts are monitored following cessation of cytotoxic antineoplastic therapy, recovery to baseline values is generally observed within three months. With regard to lymphocyte subsets, NK cell populations are frequently normal immediately following cessation of therapy [38]. These are followed by total B-cell populations, whose numbers generally normalize within one to three months [39, 40], often exhibiting an overshoot such that supranormal values may be observed for a prolonged period following completion of cytotoxic chemotherapy [38]. Restoration of total numbers of peripheral blood CD8+ T cells generally occurs within three to six months following completion of cytotoxic antineoplastic therapy, with supranormal values for this subset also frequently observed during the initial phase of regeneration [38]. Such normalization of total lymphocyte counts belies the fact that recipients of cytotoxic antineoplastic therapy frequently experience a prolonged CD4 lymphopenia. In order to understand the processes at work during this complex process of lymphocyte repopulation, we will first review the various pathways of T-cell regeneration, with an emphasis on the implications of each for restoration of host immune competence.

The ontogenic or primary developmental pathway of T-cell development involves progeny of the pluripotent hematopoietic stem cells which home to the thymus where they undergo an elaborate process involving expansion, differentiation, and selection. This process has been the focus of intense immunologic study and has been reviewed elsewhere [41]. Importantly, during the process of cell selection, the vast majority of T cells are deleted, due to either an inability to recognize antigen in the context of the host major histocompatibility complex or due to unacceptably high levels of autoreactivity. This results in a surviving population of T cells which display a TCR repertoire which is uniquely poised to recognize foreign antigens as they are encountered in the periphery. These newly produced cells are exported from the thymus bearing a naïve phenotype, and they subsequently travel throughout the peripheral lymphoid tissues awaiting encounter with antigen. While a definitive marker for such thymic emigrants does not exist, it is clear that they are contained within the CD4+CD45RA+ subset [42]. Further refinement of the subset which contains new thymic emigrants can be obtained by identifying cells which are CD4+/CD45RA+/CD62L+. Recently, a new method has been used to quantify recent thymic emigrants by employing polymerase-chain-reaction-based enumeration of cells which contain remnants of TCR rearrangement termed “T-cell receptor rearrangement excision circles” (TRECs) [42]. Thus far, however, available technology does not allow direct analysis of thymic emigrants, since analysis of cell surface expression and intracellular TRECs expression cannot be performed simultaneously.

Importantly, however, T-cell populations can be regenerated in hosts in the absence of a thymus via a process which has been termed peripheral expansion [44]. Very simply, this involves the mitotic division of mature T cells themselves, increasing their cell number. While this process can lead to dramatic increases in total-body T-cell number, it is generally unable to completely restore normal numbers of T cells, and it cannot restore TCR repertoire diversity. Indeed, because the process of peripheral expansion is driven by antigen encountered in the periphery, it is expected that contraction of the peripheral TCR repertoire will occur during the course of this process [45]. Hence, it is not difficult to understand why thymic-dependent pathways are preferred for restoration of T-cell immune competence. When vigorous, the thymic-dependent T-cell regenerative pathway can both efficiently restore normal T-cell number and provide TCR repertoire diversity. When less vigorous, thymic-dependent pathways may still play an important role in the gradual replenishment of TCR repertoire diversity over time.

In the clinical setting, the observation has been made that the degree of CD4+ depletion induced by cytotoxic chemotherapy occurs in an age-independent fashion and is related to the intensity of therapy. Importantly, however, the recovery of CD4+ T-cell populations is highly age-related, at least when evaluating children and young adults. Here, it is observed that recovery of CD4+ T-cell populations six months following completion of cytotoxic antineoplastic therapy is inversely related to age for children less than approximately 15 years of age, whereas persistent depletion is observed in older patients [46]. Significantly, this does not appear to be due to a precipitous drop in thymic function at the time of puberty but likely reflects the gradual diminution in thymic mass which is known to occur in humans during the first two decades of life [47]. Furthermore, children typically show brisk recovery of the naïve (CD45RA+) CD4+ subset coincident with recovery of total CD4+ T-cell populations, and these rises are temporally associated with radiographic evidence of transient thymic enlargement post-chemotherapy (Fig. 1). In contrast, adults generally show a slow, variable rise in CD4+ populations.
which predominantly display the memory (CD45RO+) CD4+ phenotype over the first year following cessation of antineoplastic cytotoxic therapy [34]. During subsequent years, it is not uncommon to see gradual rises in naïve (CD45RA+) CD4+ cells in adults as well, although obvious evidence of thymic enlargement is generally not observed. Therefore, thymic-dependent pathways appear capable of restoration of CD4+ T cells in children during the first six months following cessation of antineoplastic chemotherapy, whereas CD4+ T-cell recovery in adults is dependent upon the relatively inefficient thymic-independent pathways and perhaps variable degrees of low level thymopoiesis (Fig. 2). The clinical implication is that while children typically experience a relatively short period of immunosuppression associated with cytotoxic antineoplastic therapy, this period may be prolonged in adults.

These results suggest that while the cytotoxic therapy itself no doubt induces significant toxicity in thymic components, age remains the primary factor determining the capacity for the thymus to regenerate CD4+ T-cell populations following cytotoxic antineoplastic therapy. Importantly however, if children are suffering from complications such as GVHD which may further impair thymic function, they suffer from prolonged CD4+ depletion similar to that observed in adults [48]. Similarly, prolonged CD4 depletion in excess of 30 years has been observed in recipients of mediastinal irradiation for Hodgkin’s, suggesting that thymic function may be irreversibly impaired following local radiation therapy [49].

With regard to CD8+ T cells, the story is complicated by the existence of multiple CD8+ T-cell subsets, many of which recover in an age-independent fashion following cessation of cytotoxic chemotherapy. In a study of children recovering from intensive chemotherapy, it was noted that while there are significant inverse relationships between age and CD4+ regeneration as well as age and thymic enlargement as measured radiographically, no such relationships exist for CD8+ T cells [38]. Within three months following cessation of cytotoxic chemotherapy, total CD8+ numbers generally return to baseline regardless of patient age. Careful analysis of such

Figure 1. Thymic rebound as a result of chemotherapy-induced T-cell depletion in a 13-year-old patient treated for Ewing’s sarcoma. Coronal MRI T1 images of the chest are shown at time points six months following completion of chemotherapy (top) and two years following completion of chemotherapy (bottom). The thymus is observed as a bilobed structure of high signal intensity in the anterior mediastinum and is increased in size at the six-month time point but returns to baseline by two years.
populations, however, shows that the bulk of the CD8⁺ T cells contained within the recovered populations are atypical and represent the expansion of a normally minor subset of CD8⁺ T cells which lack the CD28 coreceptor. Indeed, recovery of the CD8⁺CD28⁺ subset generally does not occur until approximately one year following cessation of therapy. The CD8⁺CD28⁺ cells are typically poorly responsive to mitogenic stimuli and may function primarily as negative regulatory or suppressor populations [50-52]. Interestingly, several lines of evidence also suggest that such cells may be derived via thymic-independent pathways [53, 54]. They are typically observed in states of thymic insufficiency, such as normal aging, GVHD, HIV infection, and post-cytotoxic antineoplastic therapy. Whether they are derived via extrathymic differentiation of pluripotent hematopoietic progenitors or whether they represent terminally differentiated cells which have undergone profound antigen-driven peripheral expansion is not known. Regardless, these results illustrate that significant abnormalities in the CD8⁺ arm of the immune system likely also persist for a prolonged period following cessation of cytotoxic chemotherapy despite normalization of total CD8⁺ T-cell numbers.

**Clinical Management and Implications**

The implications of these observations for the clinical management of patients receiving cytotoxic therapy for cancer are significant. First, a risk-based approach should be used to identify high-risk groups for cytotoxic-therapy-induced immunosuppression. As discussed in the previous section, while carefully controlled studies have not been performed to distinguish various regimens for their degree of immunotoxicity, it is clear that groups at particularly high risk for cytotoxic-therapy-induced immunosuppression can be identified. Risk factors include administration of myeloablative therapies in the context of autologous or allogeneic peripheral blood transplantation or BMT. In addition, recipients of dose-intensive multiagent regimens, especially those containing high-dose cyclophosphamide (i.e., >3.5 gm/m²), purine nucleoside analogs and/or systemic corticosteroids are at risk for opportunistic complications. Patients with underlying leukemia or lymphoma and recurrent tumors are at high risk as well (Table 2).

For cancer patients deemed to be at high risk for immunosuppression, maintenance of a high index of suspicion for opportunistic infections is critical for optimal patient management (Table 3). In addition, prophylaxis for *Pneumocystis carinii* infection should be considered (Table 4). While controlled studies have not been performed in oncology populations, experience in the setting of HIV infection has shown that a peripheral blood CD4⁺ count of <200 cells/mm³ significantly increases susceptibility to this disease [19]. Based upon this information, it is rational to monitor the peripheral blood CD4⁺ T-cell counts in recipients of T-cell-depleting antineoplastic therapy to help guide decisions for instituting *Pneumocystis carinii* prophylaxis. Importantly, accurate monitoring of T-cell depletion by the use of peripheral blood CD4⁺ counts must take into account the fact that alterations in lymphocyte trafficking may result in...

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<th>Table 2. Factors increasing the likelihood of opportunistic complications</th>
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<td>Underlying disease</td>
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<tr>
<td>▲ Leukemia</td>
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<tr>
<td>▲ Lymphoma</td>
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<tr>
<td>▲ Relapsed/recurrent cancer</td>
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<tr>
<td>Myeloablative therapy</td>
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<tr>
<td>▲ Allogeneic BMT</td>
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<td>▲ Autologous BMT</td>
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<tr>
<td>Chemotherapy agents</td>
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<tr>
<td>▲ Cyclophosphamide (high dose, generally 3.6-4 gm/m²/cycle)</td>
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<tr>
<td>▲ Purine nucleoside analogs</td>
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<tr>
<td>High dose intensity</td>
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<tr>
<td>▲ Cycle compression afforded with myeloid growth factor support</td>
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<tr>
<td>Systemic corticosteroids</td>
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<td>CD4 count &lt;200 cells/mm³</td>
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<tr>
<th>Table 3. Patient management issues pertinent to recipients of immunosuppressive cytotoxic antineoplastic therapy</th>
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<tr>
<td>Optimal Management of Established Infection</td>
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<tr>
<td>▲ High index of suspicion for opportunistic infection.</td>
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<tr>
<td>▲ Aggressive management of common opportunistic infections (e.g., <em>Herpes zoster, Pneumocystis carinii</em>).</td>
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<tr>
<td>Chemoprophylaxis</td>
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<tr>
<td>▲ <em>Pneumocystis carinii</em>: recommended for patients deemed to be at high risk according to the criteria listed in Table 2.</td>
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<tr>
<td>▲ <em>Herpes simplex</em>: generally reserved for seropositive recipients of autologous and allogeneic BMT and during induction therapy for leukemia.</td>
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<td>▲ CMV: generally reserved for recipients of autologous BMT.</td>
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<td>Irradiation of Blood Products</td>
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<td>Re-immunization</td>
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<tr>
<td>▲ Primary immunization series upon recovery from T-cell depletion (generally 6-12 months for killed vaccines, 24 months for live attenuated vaccines).</td>
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<tr>
<td>Passive immunization</td>
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<tr>
<td>▲ VZIG prophylaxis following primary exposure to <em>varicella-zoster virus</em>.</td>
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<tr>
<td>▲ Intravenous immunoglobulin (IVIG): generally reserved for recipients of allogeneic BMT.</td>
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spuriously low peripheral blood CD4 counts in the absence of total-body CD4+ depletion [55]. In order to avoid this, CD4 counts should be obtained at the time of maximal hematologic recovery from ensuing cycles of cytotoxic antineoplastic therapy, and the patient should be free of infection and physiologic stress at the time CD4+ counts are measured. Whether recovery of CD4+ T-cell counts can be used to guide decisions to discontinue *Pneumocystis carinii* prophylaxis is not known, since experience in the setting of HIV infection has provided examples of opportunistic infections which have occurred following recovery of CD4 counts to a level >200 cells/mm³ [56]. This phenomenon is likely related to defects in the TCR repertoire which would be expected to persist in patients in whom recovery of T cells occurs primarily via thymic-independent peripheral expansion. An alternative is to maintain prophylaxis for 6-12 months following completion of cytotoxic therapy, since clinical experience has shown that this is the time period when patients are at greatest risk.

In addition, any evidence of varicella-zoster should be treated aggressively with appropriate antiviral therapy, and patients should be monitored closely for dissemination. Similarly, primary exposure to varicella in a patient at high risk for immunosuppression should prompt passive immunization within 96 h, as recommended [57]. All blood products should receive a dose of 2,500 cGy prior to administration to prevent post-transfusion GVHD [58]. In the setting of induction therapy for acute leukemia [59, 60] and BMT [61], results have shown that prophylaxis against herpes simplex diminishes the rate of recrudescence in patients seropositive for herpes simplex virus. Because invasive infection with cytomegalovirus is rare in the absence of allogeneic transplant [12], prophylaxis is generally not recommended for autologous BMT and dose-intensive chemotherapy recipients.

With regard to reimmunization following immunosuppressive therapy, complicating factors include the delayed recovery of the T cells and isotype repertoire limiting the likelihood of successful vaccination in patients in the months immediately following dose-intensive therapy. Because of this, it is typically recommended that patients who have undergone profound T-cell depletion receive a course of primary immunizations beginning approximately 6-12 months following completion of dose-intensive cytotoxic antineoplastic therapy. Where possible, the use of killed vaccines is preferred (e.g., IPV for immunization to poliomyelitis) with immunization with live attenuated bacterial or viral vaccines no earlier than 24 months following completion of therapy [62]. Details of this subject have been the focus of recent reviews [63, 64].

Perhaps the most important and intriguing aspect of these observations is the potential impact that cytotoxic-chemotherapy-induced T-cell depletion may have on tumor recurrence. The role of tumor surveillance in the primary prevention of tumors is an unresolved issue [65]. Similarly, it remains unknown whether T-cell immune competence can help to control or eradicate minimal tumor burdens which frequently exist following chemotherapy. In the setting of allogeneic BMT for leukemia, it is clear that immune mechanisms play a primary role in preventing disease recurrence [66]; however, it is the result of the strong allogeneic antigenic stimulus being presented to the regenerating donor immune system which drives this phenomenon. Whether similar phenomena are at work in the autologous setting where tumor antigens are no doubt much weaker is a greater source of debate.

Clearly, however, this information has profound implications for the use of actively directed immunotherapy for minimal residual neoplastic disease. Whereas animal models show clearly that such therapy is most likely to be effective if undertaken prior to the development of large bulky tumors, the practical approach for integrating T-cell-depleting therapy such as radiation therapy and chemotherapy with immunotherapy represents a substantial challenge. Current work is focused upon enhancing immune reconstitution through the use of methods to increase thymic function or through the use of adoptive transfer of T-cell populations with subsequent immunization in an attempt to skew the repertoire toward tumor-specific antigens. Toward this end, the use of lymphoactive cytokines such as interleukin 2 and interleukin 7 [67] may facilitate rapid recovery of immune competence, thus allowing the incorporation of such regimens for treatment of minimal residual neoplastic disease.

**Acknowledgments**

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![Table 4. Chemoprophylaxis regimens for *Pneumocystis carinii*](image-url)
REFERENCES


40 Storek J, Saxon A. Reconstitution of B cell immunity following bone marrow transplantation. Bone Marrow Transplant 1992;3:395-408.
45 Mackall CL, Bare CV, Titus JA et al. Thymic-independent T cell regeneration occurs via antigen driven expansion of peripheral T cells resulting in a repertoire that is limited in diversity and prone to skewing. J Immunol 1996;156:4609-4616.
63 Singhal S, Mehta J. Reimmunization after blood or marrow stem cell transplantation [see comments]. Bone Marrow Transplant 1999;23:637-646.