Acute leukemias are among the most aggressive malignancies, with doubling times as short as a few days. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are medical emergencies, typically demanding prompt treatment with intensive “induction” chemotherapy incorporating cytarabine and an anthracycline. Response rates are above 70%, as determined by morphologic examination of bone marrow aspirate. Induction is typically followed by “consolidation” chemotherapy to reduce the risk of relapse. Unfortunately, despite consolidation, many patients who enter remission subsequently relapse. Cyto- genetic or molecular features of the leukemia at diagnosis can identify those at particularly high relapse risk, as can the presence of minimal residual disease (MRD) after induction chemotherapy, determined using sensitive flow cytometric or molecular methods.

For patients considered at high risk, allogeneic hematopoietic stem cell transplantation (allo-SCT) is the only established method of preventing relapse, and is routinely recommended. Allo-SCT comprises “conditioning” chemotherapy with cytarabine or radiotherapy followed by infusion of CD34+ enriched peripheral blood leukocytes or of bone marrow aspirate from a tissue-type matched donor. This leads to immunological recognition and eradication of residual leukemic cells by donor-derived lymphocytes. Although allo-SCT can cure AML and ALL, this comes at the expense of significant toxicity and cost; treatment-related mortality is as high as 30% and graft vs. host disease or infection cause significant morbidity. Moreover, many patients are too elderly or unwell for the procedure and a suitable donor is not always available. An effective post-remission immunotherapy that can induce anti-leukemia immunity without the requirement for allo-SCT is urgently needed.

We have recently shown that irradiated autologous leukemia cells pulsed with the glycolipid invariant natural killer T (iNKT) cell agonist α-galactosylceramide (α-GalCer) can act as a simple and effective vaccine for acute leukemia. We found that while the vaccine elicited potent anti-leukemic responses, dependent on the cross-presenting Langerin+ subset of dendritic cells and both CD4+ and CD8+ T effector responses, efficacy in mice with established disease was hindered by leukemia-induced immune suppression. This suppression was attributed to an increase in the proportion of T regulatory cells, myeloid derived suppressor cells and direct suppression on effector cells by the leukemia itself, with CD4+ T cell responses more severely affected than CD8+ T cell responses.

Given the severe immune suppression induced by acute leukemia, we hypothesized that vaccination may be effective as a post-remission therapy: a window during which the leukemic burden and its suppressive effects will be reduced. Indeed, when leukemia-bearing mice were treated with cytarabine chemotherapy and subsequently vaccinated, they were fully resistant to future leukemia challenge, even when challenged with a five-fold increased dose of viable leukemia cells.

Our findings using this leukemia model are consistent with the highly immunosuppressive environment observed in humans with acute leukemia; AML is associated with increased T regulatory cell frequency and leukemic blasts inhibit effector T cells directly, via mechanisms including indoleamine 2,3-dioxygenase activity. Tumor-induced immune suppression is not restricted to leukemia, but is a barrier for effective vaccine immunotherapy in most malignancies. Alleviation of immune suppression is an area of active research and remarkable clinical efficacy has been seen with blockade of immune regulatory modulators CTLA-4 and PD-1, which are currently in clinical trials for AML and might be incorporated into the cellular vaccine approach we propose.

Although acute leukemia induction chemotherapy can suppress the immune system, recent cytarabine chemotherapy did not prevent effective vaccination in our model. Effective vaccination in patients will require both an intact iNKT cell axis and a T cell repertoire with tumor specificity. We have previously shown that iNKT cells from patients treated with
Chemotherapy for an indolent leukemia retained their in vitro ability to proliferate in response to α-GalCer treated autologous leukemia cells. Additionally, it has been reported that compared with B cells, the function of T cells is relatively preserved after AML induction chemotherapy, and T cells against leukemia-associated antigens could be expanded from >90% of children treated with chemotherapy for ALL, demonstrating a diverse T cell repertoire capable of recognizing tumor antigens can be retained after chemotherapy. Together, these findings suggest that vaccination may be a viable strategy for post-remission treatment of acute leukemia.

Advantages of a whole leukemia cell vaccine, compared with peptide or protein vaccination, include the potential to generate responses against multiple leukemia-associated antigens, including against patient-specific mutations. Importantly, this vaccine could be easily generated from patients; leukemia cells are abundant in blood and bone marrow at diagnosis and could be immunomagnetically enriched, pulsed with α-GalCer, irradiated and cryopreserved while patients proceed with induction and consolidation chemotherapy. Once in remission, the autologous leukemia cell vaccine would be administered to patients considered at high risk of relapse, but unsuitable for allo-SCT. A schema of this simple immunotherapy approach, which employs minimal ex vivo culture, is shown in Fig. 1.

In summary, we believe that vaccination with irradiated α-GalCer-pulsed whole leukemia cells may be an effective treatment for AML and ALL, and propose a strategy for its implementation in the post-remission setting.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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