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IMMUNOTHERAPY IN ACUTE LEUKEMIA

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Abstract

Recent advances in immunotherapy of cancer may represent a successful example in translational research, in which progress in knowledge and technology in immunology has led to new strategies of immunotherapy, and even past failure in many clinical trials have led to a better understanding of basic cancer immunobiology. This article reviews the latest concepts in antitumor immunology and its application in the treatment of cancer, with particular focus on acute leukemia.

History of Immunotherapy

The first successful clinical application of immunotherapy can be dated to 1796, when Edward Jenner introduced cowpox for immunization against smallpox (vaccinia), thus originating the term "vaccination".¹ Since then, major advances have been developed in the use of immunotherapy for infectious diseases, especially the introduction of numerous vaccines for the pediatric vaccination program. Some of these vaccines, such as those for hepatitis B and human papilloma virus, could indirectly or directly prevent cancer development.^{2–4}

The first direct application of immunotherapy in cancer was by William Coley in 1891, when he introduced the use of the toxins of streptococcus erysipelas and bacillus prodigiosus for the treatment of adult cancer.⁵ "Coley's toxins" were able to induce objective tumor regression in many patients, resulting in a 42% five-year disease-free survival in patients with inoperable cancers.⁶

The development of hybridoma technology in 1975 by George Köhler and Cesar Milstein for the generation of monoclonal antibodies established modern antibody therapy.⁷ Monoclonal anti-idiotypic antibody was successfully used in the early 80s by Ronald Levy to treat patients with specific B-cell lymphoma.⁸ In the late '80s and '90s, IL-2, IF- α 2a, and IF- α 2b were approved by the United States Food and Drug Administration (FDA) for the treatment of various malignancies, such as hairy cell leukemia, chronic myeloid leukemia, AIDS-related Kaposi's sarcoma, melanoma, and follicular non-Hodgkin's lymphoma. Since the approval in 1997 for the first monoclonal antibody (rituximab), many others have been developed for oncology, generating a market of over 5 billion dollars in USA sales per year.⁹

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Cancer Immunology

The first observation that the immune system may play an important role in controlling cancer development may be dated to the 1700s, when certain cancer patients who acquired and cleared bacterial infections also experienced regression of their malignancy.⁶ For many years, however, there was a lack of solid evidence to support the importance of cancer immunosurveillance in humans,¹⁰ despite increasing experimental data from animal models.^{11–16} Although general immunodeficiency has been associated with infection-associated cancer, the importance of immunodeficiency for the development of non-infection-associated cancer in human has not been firmly established.¹⁷ While some case reports of spontaneous regression of tumors such as melanoma and renal cell carcinoma may be indicative of an immune surveillance against tumor progression, these case reports were not considered strong support for his hypothesis. Several recent studies, however, powerfully suggest the importance of the human immune system in recognizing human cancer and in preventing tumor development.¹⁸ In a large study involving 905 patients transplanted with hearts or lungs who were observed between 1989 through 2004, a total of 102 new cases of cancer occurred, translating to a seven-fold higher incidence than that in the general population.¹⁹ The transplant patients were at a significant jeopardy for leukemia and lymphoma (26-fold increase in risk), head and neck cancer (21-fold), and lung cancer (9-fold). In another study of a cohort of 603 patients with colon cancer, the type, density, and location of immune cells within the resected tumor samples had more significant prognostic impact on relapse outcome than did tumor stage and nodal status.²⁰ Similar findings were observed in ovarian cancer, cervical cancer, esophageal cancer, non-small-cell lung cancer, breast cancer, urothelial carcinoma, and follicular lymphoma.^{21–28}

The most direct evidence to date was provided by a longitudinal prospective study in 3,625 healthy adults in Japan. With a median followup of 11 years, those individuals who had high baseline natural killer (NK) cell cytotoxicity against K562 leukemia cells were at much lower risk of developing various adult cancers.²⁹

The Promise of and barriers to immunotherapy

Immunotherapy for leukemia and lymphoma has drawn interest because of its non-overlapping toxicity with chemotherapy and radiation therapy and an apparent lack of long-term toxicity.^{30–32} In addition, our immune system has immense diversity, specificity, and a wide variety of effector mechanisms, involving Fas ligand, TRAIL, complement, perforin, granzyme, IF- γ , myeloperoxidase, superoxide, and nitric oxide.^{11–13,33–35} However, for the successful recognition and elimination of cancer cells by T cells, specific tumor antigens must be presented with the appropriate MHC molecules in the presence of sufficient co-stimulation. Therefore, there are numerous mechanisms by which malignant cells may escape T cell recognition.^{36–39} For instance, there may be natural selection of less immunogenic malignant cells during cancer development by antigen loss or by downregulation of MHC expression. Alternatively, costimulatory molecule expression may be downregulated.

In addition to passive immune escape, cancer cells may actively suppress the immune response.^{40–58} Mechanisms include engagement of CTLA-4 on T cells, recruitment of T regulatory cells or NKT cells to the tumor site by CCL22/17, or activating constitutively molecules such as STAT1, STAT3, or MAPK. These processes result in the secretion of a large amount of immunosuppressive soluble factors such as IL6, IL10, PGE2, VEGF, IL23, phosphatidylserine, or TGF- β . These factors can actively tolerize the immune system, by interacting with immature dendritic cells to give rise to type II helper T cells that produce IL-4 and IL-13, or by promotion of regulatory T cells, and accumulation of myeloid derived suppressor cells. The upregulation of indoleamine-2,3-dioxygenase is another common mechanism used by tumor cells to suppress

T cells and enhance T regulatory cells, by depleting tryptophan with an increase in downstream metabolites in the tumor environment.^{59,60} Tumor cells may secrete soluble Fas, Fas ligand, MHC, or NKG2D ligand to counteract both cytotoxic T cells and NK cells.^{61,62} Even after cytotoxic immune cell activation, cancer cells may still survive by defense mechanisms, such as the upregulation of serine protease inhibitor PI-9.⁶³

Immunotherapy with T Cells

Because leukemia cells may passively escape or actively inhibit the immune system, there are five essential elements for active T cell-based therapy: an immunogenic leukemia associated antigen, appropriate MHC presentation, sufficient T-cell receptor engagement, presence of co-stimulation providing the second signal, and immunological blockade of checkpoints such as CTLA-4. Recent studies have focused on maximizing these elements. Many leukemia cells express leukemia-associated antigens or leukemia-specific products, which are promising therapeutic targets, including BCR-ABL, PML-RAR α , TEL-AML1, and immunoglobulin idiotypes.^{64–75} Ex vivo induction of leukemia cells into dendritic-like cells or direct introduction of costimulatory molecules or cytokine genes into leukemia cells have been successfully performed.^{76–91} These genetically altered cells are able to induce T-cell mediated rejection in murine models, and preclinical studies have been promising. Objective response has been seen in some pilot clinical trials of active immunotherapy. In a study of ten patients (including 7 children) with high-risk acute myeloid (n = 4) or lymphoblastic (n = 6) leukemia in cytologic remission who received up to 6 subcutaneous injections of recipient-derived tumor vaccine (consisting of leukemic blasts admixed with skin fibroblasts transduced with adenoviral vectors encoding human IL-2 and CD40L), eight patients remained disease free for 27 to 62 months after treatment.⁹² In another study using autologous leukemia blasts in addition to bystander K562 transduced with GM-CSF, leukemia regression was observed in 12 of 18 patients, with reduction in the expression of WT1 transcripts.⁹³ One study used myeloid blasts transduced with the PR1 epitope of proteinase 3 enzymes; objective response was seen in 6 of the 21 patients.⁹⁴ The use of BCR-ABL P210 derived multi-peptide vaccine induced complete cytogenetic remission in 7 of 16 patients and molecular remission in three.⁹⁵ A recent investigation of WT1 peptide as a vaccine demonstrated objective responses in 12 of 20 patients.⁹⁶ In another 32 patients with non-Hodgkin's lymphoma who received idiotypic vaccination, objective responses occurred in 4 patients.⁹⁷ In 25 follicular lymphoma patients receiving idiotypic vaccines in CR2, none of the 20 patients with immune responses relapsed while undergoing vaccinations.⁹⁸ In a clinical study of 5 patients with acute myeloid leukemia treated with autologous dendritic-like leukemia cells, increased anti-leukemic T-cell responses were observed in 4 patients, although only 2 remained in remission more than 12 months post-vaccination.⁹⁹ Ongoing investigations are being conducted to augment vaccine efficacy by chemotherapy to induce apoptotic signals and to eliminate T regulatory cells.^{100,101}

In addition to active immunotherapy aimed at activating the patient's own immune system, passive immunotherapy has been pursued based on adoptive transfer of ex vivo activated immune cells.¹⁰² These manipulated cells have been successfully used for the treatment of many infectious diseases such as EBV and CMV infection in cancer patients.^{103–107} Although their applications in anticancer therapy have been less successful,^{108–112} significant progress has been made in pre-clinical studies. Various approaches have been used to augment safety and efficacy, including the introduction of suicide gene, chimeric antigen receptor, costimulatory molecule, cytokine gene, homing receptor, antitolerance receptor, or resistance genes; improvement in gene expression; induction of lymphopenia; and allodepletion.^{113–147} One difficulty with T cell therapy was that T cells must circulate, migrate through blood vessels, and home to the tumor environment.^{37,134,148} The microenvironment in the tumor cells is typically not favorable for immune response.^{37,149–150} Moreover, marrow stroma may protect leukemia cells from cell death.^{151–152}

Allogeneic bone marrow transplantation has been considered a form of immunotherapy and has benefited many more leukemia patients than all the approaches described above to date.^{153–157} The presence of graft-versus-leukemic effect has been well documented. Thus, allogeneic bone marrow transplantation may serve as a platform for T-cell based immunotherapy, especially in the setting of reduced-intensity conditioning.¹⁵⁸ Besides conventional alpha-beta T cells, gamma-delta T cells and NKT cells may also be important in the control of relapse.^{159–161} For relapse after transplantation, disease control has been observed with donor lymphocyte infusion,¹⁶² which could be combined with other therapeutic approaches such as molecular inhibitors or immunostimulatory cytokines.^{163–164}

Recently, autoreactive T cells in the setting of autologous bone marrow transplantation also have been exploited. In the COG-AHOB0121 study, patients with Hodgkin's disease who receive autologous bone marrow transplantation received cyclosporine, IL2 and -interferon for the induction of autologous graft-versus-host disease.

Immunotherapy with antibody

To date, 9 monoclonal antibodies have been approved by the FDA for the treatment of cancer; five are indicated for hematological malignancies Rituximab, Gemtuzumab ozogamicin, Alemtuzumab, Ibritumomab tiuxetan and Tositumomab.^{165–169} Many more antibodies are in development.^{170–174} Some of the major advances in biotechnology for the manufacture of monoclonal antibodies include humanization, to reduce host immunogenicity, improved pharmacokinetics, increased antibody-dependent cytotoxicity, and improved ability to fix human complement. Another advance is the ability to genetically engineer the antigen binding region CDR so as to increase affinity for the target epitope, the CH2, Fab, and Fv regions to alter antibody survival, and the Fc region to increase binding to FC- γ RIII. Arming the monoclonal antibody is possible with toxins, radionuclides, enzymes, or engineered bispecificity. Combinations of these approaches may increase the potency, reduce the toxicity, and increase the specificity of antibody treatment for cancers.

Leukemia blasts express a number of lineage-specific antigens, such as CD19, CD20, CD22, CD33, and CD52, which are excellent targets for antibody therapy. Newer antigens are being identified as potential targets for antibody therapy.^{175–176} Furthermore, antibodies are now commonly used in conjunction with other conventional approaches, such as chemotherapy, radiation therapy, or bone marrow transplantation.^{177–179}

Another use of antibody is to eliminate immunosuppressive regulatory cells rather than to affect tumor cells directly. One marketed product, ONTAK, targets the CD25 molecule expressed highly on T regulatory cells. When administered to patients with renal cell carcinoma, it enhanced the production of tumor specific CTL.¹⁸⁰

Instead of killing tumor cells or T regulatory cells, another use of antibody is direct activation of the immune system or blockade of inhibitory signals to T cells.^{165,181–183} One approach is to administer anti-CTLA4 antibody simultaneously with cancer vaccines in order to promote activation of a stronger T cell response. Unfortunately, trials conducted to date showed few long-lasting objective responses and some autoimmune manifestations such as dermatitis, enterocolitis, hepatitis, and hypophysitis.

Immunotherapy With Natural Killer Cells

The anti-cancer effect of NK cells in animals has been recognized for years and recently confirmed in humans.^{33,184–187} NK cells appear to be good candidates for immunotherapy for cancer, as they fulfill all the 7 selection criteria, including speed of action (cytotoxic in minutes without prior sensitization), potency (tumoricidal rather than tumorigenic), broad specificity

(distinguish normal cell from cancer cell but do not require different preparations for different tumor types), potential for optimal donor selection (laboratory assay available), ease of preparation and administration (technology easily exportable), lack of side effects (they do not cause graft-versus-host disease or organ toxicity), and complementary to other approaches (can be administered together with antibodies, cytokines, bone marrow transplantation, or gene therapy).

NK cells use a sophisticated network of receptors on the cell surface to determine within seconds whether the target cells should be killed.¹⁸⁸ These receptors are typically classified based on their function as inhibitory receptors, activating receptors, or co-receptors. While the inhibitor receptors are responsible for “missing-self” and “modified-self” recognition, the activating and co-receptor are responsible for “induced-self” recognition. Cancer cells in cycle have been shown induce a more potent NK cell response.¹⁸⁹ In addition, induction of DNA damage can trigger an ATM response, thus resulting in increased expression of NKG2D ligand and increased susceptibility to NK cells.¹⁹⁰ The selection of an optimal NK cell donor is now possible due to the availability of KIR typing.¹⁹¹ KIR studies have shown that not all individuals express all KIR genes, and many donors do not express a KIR product because either the KIR gene is absent, or it is expressed at a lower level, or the allele cannot be expressed. Inhibitory KIR-HLA receptor-ligand mismatch has been demonstrated to reduce the risk of relapse after bone marrow transplantation in many studies, including those using haploidentical donors, matched unrelated donors, HLA identical sibling donors, and in autologous transplantation.^{192–195} Large scale isolation of purified NK cells is now feasible, and the product has minimal contamination of T cells and B cells, thus eliminating the risk of graft-versus-host disease or EBV-induced lymphoproliferative disease.¹⁹⁶ With a single apheresis product, the yield of NK cells could typically be more than 100 million. These purified cells have extensive proliferative capacity in murine models, and are detectable in recipients for approximately one month.¹⁹⁷ Cells can also be expanded in large numbers using K562 cells transduced with 41BB ligand and transmembrane IL15 molecules.¹⁹⁸ Specificity of NK cells may further be increased by chimeric antigen receptors such as anti-CD19. NK cells do not cause graft-versus-host disease; indeed, they may reduce its risk by attacking the recipient’s dendritic cells. A multipronged approach could be used to augment the function of NK cells, including the use of cytokine, 41BB ligand, toll-like receptor, chimeric receptor, tumor antibody, or KIR receptor antibody.^{192,196–205} Adoptive transfer of NK cells has been implemented clinically for the treatment of high- risk leukemia either immediately following conventional stem cell transplantation, as a consolidation therapy following standard chemotherapy, or for the induction of remission for leukemia refractory to chemotherapy.

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