Cancer Chemother Pharmacol (2000) 46 (Suppl): S18–S22

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Targeted therapy of acute myeloid leukemia with monoclonal antibodies and immunoconjugates

Abstract Traditional chemotherapy for acute leukemia often causes life-threatening toxic effects due to a lack of specificity for hematopoietic cells. Monoclonal antibodies and fusion proteins that target cell surface antigens on leukemic blasts are being evaluated for their cytotoxic effects and as a means of delivering chemotherapeutic agents or radiation directly to malignant cells. It is hoped that this strategy might selectively ablate malignant cells without many of the toxic effects commonly associated with conventional chemotherapy. In acute myeloid leukemia (AML), the cell surface antigens CD33 and CD45 are especially suitable targets. Although CD33 is expressed on AML blast cells from about 90% of patients, normal hematopoietic stem cells lack this antigen, as do essentially all nonhematopoietic tissues. For that reason, anti-CD33 antibodies have been created to target malignant myeloid and immature normal cells selectively while sparing normal stem cells. Anti-CD33 antibodies have also been used to deliver radiation or a cytotoxic agent directly to leukemic cells. Since the vast majority of leukemias and normal stem cells express the cell surface antigen CD45, another targeting approach allows the delivery of myeloablative radiation to bone marrow and spleen, common sites of leukemic involvement. Consequently, ^{131}I-labeled anti-CD45 antibody has been combined with traditional preparative regimens for patients receiving bone marrow transplantation for acute leukemia. Finally, fusion proteins such as those combining diphtheria toxin with granulocyte-macrophage colony-stimulating factor (GM-CSF) to target the GM-CSF receptor are now being evaluated in clinical trials. Both unconjugated and conjugated antibodies have shown promise in early clinical trials, and may represent appealing therapeutic alternatives for patients with AML.

Key words Acute myeloid leukemia · Acute myelogenous leukemia · Monoclonal antibody · Immunotoxin · Immunoconjugate

Introduction

Conventional chemotherapeutic treatments of acute leukemias are often life threatening due to a lack of specificity for hematopoietic cells. It is possible that approaches that specifically target leukemic blast cells might be safer, and possibly more effective, than the use of current nonspecific chemotherapeutic agents. Leukemia-specific antigens are uncommon, however. Therefore most monoclonal antibody targeting approaches have been directed against normal hematopoietic cell surface antigens that are also expressed by leukemic blast cells. Nonspecific binding to most normal tissues is typically avoided with this approach.

Unconjugated monoclonal antibody

While unconjugated antibodies to CD20 in non-Hodgkin lymphoma and Her-2-neu in breast cancer have been shown to be effective therapies, comparable strategies in acute leukemia have met with less success. Some data suggest that the substantial tumor regressions seen in non-Hodgkin lymphoma in association with anti-CD20 antibodies may be mediated more by a direct initiation of apoptosis than by antibody-dependent cellular cytotoxicity [22]. For this reason, comparable efforts to

Work presented at the 15th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "New Immunological Approach to Cancer Treatment," 10–11 September 1999, Nagoya, Japan

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identify a similar protein on the surface of acute myeloid leukemia (AML) cells would be worthwhile.

Unconjugated anti-CD33 antibody

As cells mature in the myeloid lineage, pluripotent hematopoietic stem cells give rise to progenitors with diminished self-renewal capacity and a greater degree of differentiation. During this development, normal myeloid cells express distinct cell surface antigens including CD33 [2, 10, 12]. The myeloid cell surface antigen CD33 is an attractive target for monoclonal antibodies, as it is expressed on AML blast cells from about 90% of patients [10, 12]. While the CD33 antigen is present on maturing normal hematopoietic cells and on AML cells, normal hematopoietic stem cells lack this antigen [1]. In addition, selective ablation of $CD33^+$ cells from leukemic marrow aspirates from some patients with AML resulted in the growth of normal, nonclonal granulocytes and monocytes in a long-term bone marrow culture system [4, 5]. These findings suggest that clinical responses might be achieved by selectively targeting and eliminating $CD33^+$ cells.

In early studies, investigators at Fred Hutchinson Cancer Research Center, Seattle, WA, and Memorial Sloan-Kettering Cancer Center, New York, NY, administered approximately 5 mg/m^2 of trace radioiodinated anti-CD33 antibodies to patients with refractory or relapsed AML [3, 21]. Although rapid saturation of leukemic blast cells in peripheral blood and marrow was observed after intravenous infusion of the antibody, no significant clinical responses were seen using these early approaches. More recently, supersaturating doses of humanized antibody to the CD33 antigen (HuM-195) have been evaluated [7]. Patients received between 12 and 36 mg/m^2/day on days 1 through 4, which was then repeated on days 15 through 18. Ten patients with relapsed or refractory myeloid leukemias (nine AML and one chronic myelogenous leukemia [CML]) were treated in this manner. While only one patient achieved complete remission, a decrease in leukemic burden was observed in three patients. Five patients had progressive disease, and treatment response was inevaluable for one patient. Before receiving treatment with the anti-CD33 monoclonal antibody, the patient who achieved complete remission had 8% blasts in his bone marrow after two cycles of induction therapy with idarubicin and cytarabine.

In a follow-up study using similar supersaturating doses of HuM195, 35 patients received a total of four courses of antibody therapy [11]. Among the 15 patients who had less than 30% blasts in their bone marrow prior to antibody treatment, two complete responses were reported. Since remissions were obtained in patients with low tumor burdens and the therapy was relatively nontoxic, this approach using an unconjugated antibody may prove to have a role in postchemotherapy consolidation therapy in patients in whom minimal residual disease is detected.

For patients in complete remission harboring minimal residual disease, some clinical efficacy has been observed in acute promyelocytic leukemia (APL) [15]. Fifteen APL patients who achieved complete remission after induction therapy with all-*trans* retinoic acid (ATRA) received HuM-195 3 mg/m^2 twice weekly for 3 weeks. The patients then received idarubicin and cytarabine consolidation therapy, and an additional 6 months of maintenance HuM-195 given monthly in two doses separated by 3 or 4 days. Bone marrow aspirates were evaluated serially for the PML/RAR-α mRNA by reverse-transcription polymerase chain reaction (RT-PCR). While only one of 15 patients was PCR negative after ATRA alone, five of 13 evaluable patients (38%) became PCR negative after receiving the first 3-week course of HuM-195. Following conventional chemotherapy consolidation, all 11 patients who were evaluable had no evidence of disease by RT-PCR. Although it is conceivable that the four additional patients might have achieved PCR negativity without Hu-M195 treatment due to a delayed effect of ATRA, these data suggest a therapeutic role for antibody therapy, particularly in patients with low tumor burden.

Unconjugated antibody to GM-CSF

Some leukemias have been noted to produce GM-CSF spontaneously. Acting on the hypothesis that some leukemic growth might be regulated in an autocrine manner, investigators from Marseille studied anti-GM-CSF antibody in eight patients with AML [6]. Although the antibody therapy was well tolerated, no clinically significant antileukemic responses were documented [6].

Immunoconjugates, immunotoxins, and fusion proteins

For the past several years, antibodies have been evaluated as a means of specifically delivering cytotoxic agents to leukemic blast cells. Some cell surface antigens (e.g., CD45) remain on the cell surface upon binding with antibody or a fusion protein, while others (e.g., CD33) internalize. This latter phenomenon of "modulation" affords an opportunity to deliver a cytotoxic agent to the interior of a leukemic blast cell. Antigens expressed only on maturing myeloid cells (e.g., CD33) are particularly appealing for this approach since the pluripotent hematopoietic stem cell can be spared. A similar approach consisting of GM-CSF ligand associated with diphtheria toxin targets the receptor for GM-CSF expressed by most myeloid leukemias [14, 19].

Conjugated anti-CD33 antibody

Administration of anti-CD33 antibody results in rapid saturation of CD33 sites throughout the body, followed by rapid internalization (modulation) of the antigen–

antibody complex by the cell [3, 21]. As a means of taking advantage of this behavior, the potent antitumor antibiotic calicheamicin was linked to a humanized anti-CD33 antibody to create the investigational agent CMA-676 (recently named gemtuzumab ozogamicin) [13]. In collaboration with Wyeth-Ayerst Research, Philadelphia, PA, and the City of Hope National Medical Center, Duarte, CA, we at the Fred Hutchinson Cancer Research Center conducted a phase I study of this agent. Patients with relapsed or refractory $CD33^+$ AML were treated with escalating doses of the drug every 2 weeks for three doses [23]. Leukemia was eliminated from the blood and marrow of eight (20%) of 40 patients and blood counts normalized in three (8%) patients. A postinfusion syndrome of fever and chills was the most common toxic effect after the intravenous infusion of drug conjugate. Otherwise, gemtuzumab ozogamicin doses up to 9 mg/m^2 were generally well tolerated. Modest and reversible hepatic transaminase elevation and hyperbilirubinemia were observed in some patients who received gemtuzumab zogamicin at the 6 and 9 mg/m^2 dose levels. No patients experienced clinically significant cardiac, renal, or neurologic toxic effects.

In the subsequent phase II study, the 9 mg/m^2 dose level was selected because consistently >75% of CD33 sites were saturated at this dose and nonhematologic toxicity was not considered to be dose limiting in the phase I study. In this study, patients with AML in first untreated relapse after a period of at least 6 months were treated with two doses of gemtuzumab ozogamicin 9 mg/m^2 every 2 weeks [24]. Of the 45 patients, 17 (38%) achieved remission characterized by <5% blasts in the bone marrow, >1500 neutrophils/mm^3, and platelet transfusion independence. At the time of the report, 13 of 17 responding patients remained in remission at a median of 163 (range 17–471) days after receiving gemtuzumab ozogamicin. While other clinical studies have documented frequent immune responses after administration of murine-derived monoclonal antibodies or naturally occurring toxins, no patients in the phase II study developed a positive immune response to the drug conjugate.

Radiolabeled antibodies

In the context of hematopoietic stem cell transplantation (HSCT), the common hematopoietic cell surface antigen CD45 has been targeted for the delivery of radiation. The rationale for this approach derives from two prospective randomized studies from the Fred Hutchinson Cancer Research Center suggesting that higher doses of radiation given the HSCT preparative regimen appear to be associated with a decreased rate of subsequent leukemic relapse. In these studies, patients with AML in first remission [8] and CML in chronic phase [9] received cyclophosphamide and either 12 Gy or 15.75 Gy total body irradiation (TBI) followed by human leukocyte antigen (HLA)-matched related bone marrow transplantation. In both studies, a lower risk of subsequent relapse (12% vs. 35% for AML, 0% vs. 25% for CML) was associated with the delivery of a higher TBI dose. Unfortunately, since a higher rate of transplant-related mortality was observed in the patients who received the higher TBI dose, no significant difference in disease-free survival was observed in either study. Since a radiation dose-response effect appears to exist for myeloid leukemias, radiolabeled monoclonal antibodies have been evaluated as a means of augmenting doses of radiation to sites of leukemia including marrow and spleen without increasing transplant-related mortality.

^{131}I-labeled anti-CD33 antibody

In a pilot study at the Fred Hutchinson Cancer Research Center, ^{131}I-labeled anti-CD33 (p67) antibody was administered to patients with AML beyond first remission or refractory to conventional therapy [3]. Each patient's biodistribution was evaluated after delivering a test dose of trace iodine-labeled antibody as a means of estimating the radiation dose delivered to bone marrow and spleen in comparison with other vital organs. Patients received a therapeutic dose of ^{131}I-labeled anti-CD33 antibody combined with cyclophosphamide followed by TBI and bone marrow transplantation if the amount of radiation delivered to bone marrow and spleen was greater than that delivered to liver, lung, or kidney. While it was learned that CD33 sites could be saturated with antibody doses of greater than 5 mg/m^2, favorable biodistribution was only observed in four of nine patients. In addition, after the ^{131}I-labeled anti-CD33 antibody–antigen complex internalized, ^{131}I was severed from the antibody and rapidly excreted into the circulation. Since an insufficient degree of antibody-targeted radiation was actually achieved, this approach was abandoned in favor of targeting CD33 with gemtuzumab ozogamicin (described above).

^{213}Bi-labeled anti-CD33 antibody

Investigators at Memorial Sloan-Kettering Cancer Center have taken an alternative approach to targeting the CD33 antigen with radiation [16]. In contrast to ^{131}I, ^{213}Bi emits an alpha particle that produces a shorter path length and briefer half-life. For this reason, it was hypothesized that effective leukemic blast cell targeting might be attained without substantial nonspecific cytotoxicity. In a phase I study, 17 patients with relapsed (n = 13) or refractory (n = 3) AML and one patient with chronic myelomonocytic leukemia received escalating doses of ^{213}Bi HuM-195 in three to six fractions over 2 to 4 days. Patients tolerated this therapy reasonably well, and myelosuppression lasting 8–34 days was observed. Specificity for bone marrow, liver, and spleen was seen within 10 min of drug infusion by

gamma camera images. Although 10 of 12 evaluable patients had reductions in leukemic blast cell counts in peripheral blood, and 12 of 17 patients had reductions in the percentages of marrow blasts, no complete remissions had been documented at the time of the report.

^{131}I-labeled anti-CD45 antibody followed by HSCT

The CD45 cell surface antigen also represents a desirable target for radiolabeled antibody therapy. In contrast to CD33, it is expressed at high levels by almost all white blood cells and their precursors, including the vast majority of acute myeloid and lymphoblastic leukemias. While CD33 internalizes upon antibody binding, antibody-bound CD45 antigen tends to remain on the surface of cells. Hence antibody-delivered ^{131}I is less liable to be cleaved and released systemically. Since CD45 is expressed universally by white blood cells in addition to leukemic cells, ^{131}I-labeled anti-CD45 antibody can be used in patients in remission as well as in active relapse.

Two clinical studies of this agent have been performed in combination with conventional preparative regimens for patients receiving marrow transplantation for acute leukemia at the Fred Hutchinson Cancer Research Center. In the first study, 44 patients with high-risk acute leukemias and advanced myelodysplastic syndromes received escalating doses of ^{131}I-labeled anti-CD45 antibody combined with cyclophosphamide and TBI followed by bone marrow transplantation [17]. A dose of ^{131}I calculated to deliver from 3.5 Gy to a maximum of 12.25 Gy to the normal organ receiving the highest dose was administered. In comparison with the experience with anti-CD33, 84% of patients who received ^{131}I-labeled anti-CD45 antibody had a higher amount of radiation delivered to bone marrow and spleen than to other vital organs. Thus most patients had a favorable biodistribution of ^{131}I-labeled anti-CD45 antibody.

In the dose-escalation study, severe mucositis was observed in two patients treated with 12.25 Gy, thus defining this level as unacceptably toxic. A total of six patients were treated with 10.5 Gy, and one experienced grade III venoocclusive disease of the liver. While the patient recovered, 10.5 Gy was defined as the maximum tolerated dose. This study demonstrated that at least twice as much radiation could be delivered to the target organs of bone marrow and spleen compared to the normal organ receiving the highest dose. From the time of transplant, seven of 25 treated patients with AML or myelodysplastic syndrome remained disease-free for 15–89 months (median 58 months).

This approach was also studied by combining ^{131}I-labeled anti-CD45 antibody with a busulfan and cyclophosphamide preparative regimen [17, 18]. A cohort of 25 patients with AML in first or second remission or early first relapse received up to 260 mCi associated with bone marrow doses of 6–16 Gy. Ninety percent of patients evaluated for protocol entry had favorable biodistribution. Currently, 18 of the 24 patients with AML in first remission are surviving disease-free 10–63 months (median 42 months) after transplantation. Four patients died from transplant-related causes, and only two patients experienced relapse. Since a much higher relapse rate would have been anticipated for a similar cohort of patients with AML conditioned with busulfan and cyclophosphamide and transplanted in first remission, the addition of targeted radiation is beginning to show significant promise.

Current studies

Since unconjugated humanized anti-CD33 antibody appears able to eradicate a limited number of leukemic blast cells from patients with AML, it may prove to have a role in the treatment of patients with minimal residual disease. As a means of improving the capability of antibodies to eliminate tumor, potent cytotoxic agents or radioisotopes have been conjugated to monoclonal antibodies to augment targeted cytotoxicity. When used as a single agent in patients with AML in first relapse, humanized anti-CD33 antibody linked to the potent antitumor antibiotic calicheamicin (gemtuzumab ozogamicin) safely induced remission in 40% of patients. Given the lack of clinically significant, nonhematologic toxic effects, gemtuzumab ozogamicin is likely to be studied as a replacement for anthracycline in combination chemotherapy regimens and combined with existing conditioning regimens for HSCT. Studies are currently underway evaluating gemtuzumab ozogamicin in pediatric and elderly patients, and it is anticipated that this agent will be studied in the setting of newly diagnosed and minimal residual disease as well.

The radioisotope immunoconjugate ^{213}Bi HuM-195 reduces tumor burden in patients with AML, but it is not known whether remissions can be achieved with acceptable toxicities. Clinical trials evaluating the potential efficacy of this agent in relapsed and refractory AML are ongoing. In the context of a bone marrow transplantation preparative regimen, ^{131}I-labeled anti-CD45 antibody has been shown to deliver a much higher dose of radiation to bone marrow and spleen than to other vital organs. With relapse occurring in only two of 24 patients with AML in first remission treated in this manner, this approach appears to have significant clinical efficacy. Currently, phase II HSCT studies with both HLA-matched related and unrelated donors using ^{131}I-labeled anti-CD45 antibody are being performed for patients with advanced acute leukemias.

Future directions

Since the clinical efficacy of unconjugated anti-CD20 antibody in lymphoma appears to be related to interruption of signal transduction events leading to apoptosis, comparable targets may be present in acute

leukemias. For example, monoclonal antibodies might be created against a variety of growth factor receptors or other surface antigens that regulate cellular maturation and proliferation. It is possible that simply blocking the binding of growth factor might be sufficient to impede cell division in some leukemias. In other leukemias, cell surface receptors that induce apoptosis might be targeted [20].

Acknowledgement The author is supported by an American Cancer Society Clinical Oncology Career Development Award.

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