New Strategies in Radioimmunotherapy for Lymphoma

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Treatment options for patients with indolent non-Hodgkin's lymphoma historically involved radiation or chemotherapy. Although initial response rates are excellent, treatment is increasingly less effective with each successive relapse. The advent of immunotherapy heralds a new era for the treatment of these patients. Radioimmunotherapy adds the benefits of cytotoxic radiation to immunotherapy and represents a significant addition to the treatment armamentarium. Various antigens for lymphoma have been targeted, of which anti-CD20 antibodies are the furthest in development. Ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals, San Diego, CA), a ^{90}yttrium-labeled agent, and ^{131}iodine-labeled tositumomab (Bexxar; Corixa, Seattle, WA) are approved by the US Food and Drug Administration. Both agents have shown utility in therapy for relapsed and refractory low-grade and transformed lymphomas. This review highlights features of radioimmunotherapy that are relevant to non-Hodgkin's lymphoma, focusing on the two anti-CD20 antibodies.

Introduction

Non-Hodgkin's lymphoma (NHL) is the fifth most common malignancy in the United States. An estimated 53,400 new cases of NHL are expected in the year 2003, with 23,400 deaths [1]. Although the World Health Organization classification identifies over 30 subtypes of NHL [2], it remains clinically relevant and helpful to categorize the lymphomas as diffuse or follicular and low-grade (or indolent), intermediate, or high-grade based on their untreated natural history.

The most common forms of NHL are diffuse large B-cell lymphoma (31%) and follicular lymphoma (22%) [3]. Whereas diffuse large B-cell lymphomas (intermediate grade) are potentially curable with combination chemotherapy regimens [4], indolent or low-grade lymphomas such as follicular NHL generally present in advanced stage and are considered incurable with current therapies.

The treatment of indolent disease is determined by its clinical presentation and stage. Frequently, patients with a low disease burden can be expectantly monitored for some length of time. However, the majority of patients ultimately require systemic therapy as the disease course follows a cyclic pattern of remission and recurrence, with progressively shorter remission intervals. Unfortunately, despite numerous treatment options, including radiotherapy for localized disease, single-agent and combination chemotherapy, biologic therapy, and bone marrow transplantation, the median survival (7–10 years) for indolent lymphomas has remained unchanged for over three decades [5].

Recently, the development of the chimeric mouse–human monoclonal antibody rituximab (Rituxan; Genentech, South San Francisco, CA) has had a major impact on the treatment of B-cell NHL. Directed against the B lymphocyte–specific antigen CD20, almost ubiquitously overexpressed in malignant B-cell lymphomas, rituximab has demonstrated significant single-agent activity in follicular lymphoma, with response rates of 50% to 70% and a median response duration of approximately 12 months [6–9]. When rituximab is combined with chemotherapy, response rates in indolent lymphoma of 93% to 95% are frequently obtained [10,11]. A randomized phase III trial in elderly patients with diffuse large B-cell lymphoma combining rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) demonstrated improved survival [12]. Unfortunately, a survival benefit has not yet been demonstrated in indolent lymphomas, and most patients continue to have inevitable relapses. Consequently, there is a continuing need for new and effective agents to treat indolent lymphomas.

Radiolabeled monoclonal antibodies represent a new and effective addition to the treatment armamentarium. Melding the benefits of monoclonal antibody therapy with those of radiotherapy, radioimmunotherapeutic agents have proven to be safe and efficacious, capable of directly targeting B cells and causing cell death either through immunobiologic mechanisms or as carriers of cytotoxic agents. These agents include such toxins as ricin and such radionuclides as ^{131}iodine (^{131}I) and ^{90}yttrium

(^{90}Y). In February 2002, the US Food and Drug Administration (FDA) approved ^{90}Y-ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals, San Diego, CA) for use in patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL, including follicular lymphoma refractory to rituximab. On June 27, 2003, ^{131}I-tositumomab (Bexxar; Corixa, Seattle, WA) received approval from the FDA for the treatment of CD20-positive follicular NHL, with or without transformation, which is refractory to rituximab and has relapsed following chemotherapy. Both agents are murine antibodies directed against the CD20 antigen expressed on the surface of normal and malignant B lymphocytes and deliver radiation to the targeted and neighboring cells. This article reviews the characteristics of these two agents and the clinical trials leading to their approval, as well as highlighting ongoing trials with these agents and other new radioimmunoconjugates in clinical development.

Ibritumomab Tiuxetan

Ibritumomab is a murine IgG kappa monoclonal antibody that binds specifically to the CD20 antigen expressed on B cells; it is the parent murine antibody of the chimeric murine–human monoclonal antibody rituximab [13]. The antibody is available for conjugation via the chelate tiuxetan with the radiometals ^{111}indium (^{111}In) or ^{90}Y. With the use of a murine antibody, the clearance of the antibody via the reticuloendothelial system is accelerated, thus limiting prolonged total-body irradiation. Furthermore, tiuxetan forms a stable thiourea covalent bond with the radiometals, limiting dissociation of the radionuclide from the antibody.

^{90}Yttrium is a pure beta emitter with a maximum energy of 2.28 MeV and a pathlength of 5.3 mm [13]. The physical half-life of ^{90}Y is 64.1 hours, with an effective plasma half-life of 27 to 30 hours [13]. Once bound, ^{90}Y is capable of delivering cytotoxic radiotherapy not only to the target cell but also to the neighboring cells, creating a cross-fire effect [14–16]. The therapeutic activity of the agent appears to be a combination of apoptosis induction, antibody-dependent cellular toxicity, and complement-mediated cell lysis mediated by rituximab [17,18] along with radiolysis caused by ^{90}Y. ^{111}In is a radiometal with a physical half-life of 68 hours and gamma emissions of 171 and 245 KeV, permitting external imaging using gamma cameras. Preclinical studies have demonstrated that biodistribution of ^{90}Y-ibritumomab tiuxetan is adequately predicted by ^{111}In-labeled antibody [19].

Radioimmunotherapy with ibritumomab tiuxetan is carried out in two phases, an imaging phase and a therapeutic phase. The first phase consists of an infusion of rituximab (250 mg/m^2) followed by an imaging dose of 5 mCi of ^{111}In-labeled ibritumomab tiuxetan. Whole-body gamma camera imaging is subsequently performed at selected time points (typically 2–24 hours after infusion and again 48–72 hours after infusion) to ensure acceptable biodistribution of the radioimmunoconjugate (a third image, obtained 90–120 hours after infusion, can be performed if necessary).

Three major elements determine favorable biodistribution. The first image (after ^{111}In-labeled ibritumomab tiuxetan) should demonstrate adequate distribution of radioactivity throughout the blood pool, which decreases in subsequent images. Hepatic and splenic uptake of radioactivity is moderate or high, and it usually appears relatively greater in the subsequent images; there should be minimal radioactivity in the kidneys and other normal organs. Finally, tumor targeting, visualized as increased radioactivity in areas of known tumor, is desirable but not mandatory for clinical response. Unfavorable biodistribution is rare and usually manifests as increased radioactivity in kidneys, bowel, or lungs, with no tumor targeting.

The second phase, a week later, consists of another infusion of rituximab, 250 mg/m^2, followed by a therapeutic dose of ^{90}Y-labeled ibritumomab tiuxetan, 0.3 to 0.4 mCi/kg, up to a maximum dose of 32 mCi. Administration of the cold antibody before radioimmunotherapy diminishes nonspecific binding to circulating CD20+ B cells, improving biodistribution and tumor targeting, and theoretically saturates peripheral CD20 sites on bulky tumors, allowing greater penetration of the radioimmunoconjugate dose.

Pharmacokinetics and dosimetry

A summary of dosimetry and pharmacokinetic data in 179 patients from four clinical trials proved that treatment with ^{90}Y-ibritumomab tiuxetan could be given safely to patients with refractory and relapsed NHL with adequate bone marrow reserve and less than 25% bone marrow involvement, based on a fixed weight-adjusted dosing schedule [20•]. The median radiation-absorbed doses to critical organs were below normal limits, with 2.11 Gy to lungs, 4.5 Gy to liver, 7.42 Gy to spleen, 0.23 Gy to kidneys, 0.62 Gy to red marrow, and 0.57 Gy to total body; urinary excretion of the administered dose is only 9.2% [20•]. Delivered dose to tumor was estimated in the phase III study to be 1484 Gy [21].

Using blood-derived and sacral count–based methods for dose estimation, dosimetric parameters were evaluated as possible predictors of toxicity [20•]. Hematologic toxicity did not correlate with dosimetry or pharmacokinetic results, nor was there correlation between hematologic toxicity and red marrow radiation-absorbed dose. Consequently, baseline blood count, as an indicator of marrow reserve, and extent of marrow involvement assessed on bilateral biopsies remain adequate parameters for patient selection for nonmyeloablative treatment. The investigators concluded that dosimetry estimation with ^{111}In-ibritumomab tiuxetan images should not be used for adjustment of administered radioactivity. They adopted a weight-based dosing schedule that correlates better with toxicity. Dosimetry is therefore not required before therapy in the defined patient population; imaging is carried out to exclude an altered biodistribution that may predict increased toxicity [20•].

Phase I and II clinical trials

The initial dose-finding phase I/II study with ibritumomab tiuxetan demonstrated the expected dose-limiting toxicity to be reversible myelosuppression, predominantly thrombocytopenia and neutropenia. This study enrolled 51 patients with low- or intermediate-grade or mantle cell lymphoma and established the maximum tolerated dose to be 0.4 mCi/kg in patients with platelet counts greater than 150,000/μL, and 0.3 mCi/kg in patients with platelet counts between 100,000 and 150,000/μL. The overall response rate (ORR), constituting 26% complete (CR) and 41% partial responses (PR), was 67%. The Kaplan-Meier estimates of time to disease progression in responders and duration of response were 12.9+ and 11.7+ months, respectively [22]. A follow-up open-label, single-arm phase II study in 30 patients with relapsed or refractory low-grade or transformed NHL with mild thrombocytopenia (100–149 K) confirmed the effectiveness of the 0.3 mCi/kg-dose regimen, with an ORR of 83% (CR=37%; unconfirmed CR=6.7%; PR=40%). The median time to progression was 9.4 months [23].

The initial studies revealed encouraging responses in transformed and intermediate-grade lymphomas. This experience, spanning four trials, was summarized by Bartlett *et al.* [24]. Of 15 patients with transformed indolent lymphoma in these studies, the ORR was 53% (13% CR; 40% PR). The median time to progression was 8.5 months, and two patients continued to be in remission at 30 months. These data suggest that treatment with ibritumomab tiuxetan may be effective and safe in patients with transformed B-cell NHL.

Phase III clinical trials

In the pivotal study for registration, a phase III randomized, controlled trial of 143 patients with relapsed or refractory low-grade, follicular, or CD20-positive transformed B-cell NHL, ibritumomab tiuxetan combined with rituximab had a higher ORR compared with rituximab alone (80% vs 56%). The CR rate with ibritumomab tiuxetan was also higher than that of rituximab alone (30% vs 16%) [25].

In another trial, 54 patients with follicular NHL who were refractory to rituximab were evaluated for response, using the patient's last rituximab or chemotherapy response as an intrapatient comparator. Ibritumomab tiuxetan therapy resulted in an ORR rate of 74%, with 15% of patients achieving CRs and significant improvements in duration of response compared with the patient's last rituximab response [26•].

At the 2003 annual meeting of the American Society of Clinical Oncology (ASCO), Witzig *et al.* [27] presented updated data demonstrating the durability of response with ibritumomab tiuxetan for the 28% of patients achieving ongoing CRs. The median duration of response was greater than 45 months.

Side effects and contraindications

Toxicity associated with ibritumomab tiuxetan is primarily hematologic, transient, and reversible. No dose-limiting nonhematologic toxicity has been observed. In patients with limited marrow reserve, manifested primarily by thrombocytopenia, a reduced dose (0.3 mCi/kg) of ibritumomab tiuxetan has been found to be safe and effective, with a toxicity profile comparable with that of patients with normal platelet counts [23].

The safety data on 349 patients in five studies of relapsed, low-grade, follicular, or transformed NHL were recently published [28]. Data are available from a follow-up period of 4 years after therapy or progression of disease. Typical grade 1 or 2 toxicities related to rituximab infusion were seen, with no significant organ toxicities. The peak hematologic toxicity was observed at 7 to 9 weeks and lasted for 1 to 4 weeks. Incidents of grade 4 neutropenia, thrombocytopenia, and anemia occurred in 30%, 10%, and 3% of patients, respectively, in those taking 0.4 mCi/kg, compared with 35%, 14%, and 8%, respectively, in those taking 0.3 mCi/kg [28]. Ibritumomab tiuxetan should be used with caution, if at all, in patients who have significant marrow impairment, either by disease or by prior therapy. Patients with more than 25% marrow involvement by disease; a platelet count less than 100,000/μL; an absolute neutrophil count less than 1500/μL; prior bone marrow transplant (either autologous or peripheral stem cell); hypocellular marrow (less than 15% cellularity or a marked reduction in bone marrow precursors); or a history of failed stem cell collection are not candidates for this therapy. These patients have been excluded from all trials.

Similarly, patients with a history of type 1 hypersensitivity or anaphylactic reactions to murine proteins are not suitable candidates. In contrast to most studies with murine monoclonal antibodies, the frequency of an immune response (determined by the development of serum human antimouse antibodies [HAMA]) has been very low (< 2%) in studies with ibritumomab tiuxetan [28]. This low level of response may be due to predosing with a chimeric (rather than murine) antibody, thus limiting murine exposure, or to the impaired ability of the immune system to mount a response to the xenogenic protein due to disease or treatment-related effects. In the combined safety data, the incidence of myelodysplasia and acute leukemia with ibritumomab is 1%, though the follow-up is short [28].

Radiation safety

The antibody is administered as a slow intravenous bolus after completion of rituximab infusion using precautions for radiation safety. Neither radiation isolation nor lead shielding is needed. Both infusions can be carried out as an outpatient procedure. Because of the short half-life and short penetration of beta emissions, patients have no significant limitations of activities after dosing [13].

Labeling of radiometal to the conjugated antibody can be accomplished in a well-equipped radiopharmacy. The radioimmunoconjugate is also available as a prepared product from a centralized radiopharmacy.

Tositumomab

Tositumomab is an IgG2a murine monoclonal antibody conjugated with ^{131}I and given with cold murine tositumomab. The antibody binds only to CD20-positive cells and not to other hematopoietic or nonhematopoietic tissues. ^{131}I emits beta particles, with a pathlength of 0.8 mm and beta energy of 0.606 mEV, and gamma emissions with an energy of 0.364 mEv [29]. The therapeutic activity of the antibody is due to antibody-dependent cellular toxicity and complement-mediated cell lysis, combined with ^{131}I radiotherapy [30,31]. The antibody targets selectively to CD20-bearing lymphocytes, limiting exposure to normal tissues; however, as with ibritumomab, surrounding normal or malignant cells that do not express antigen may also be affected by radiation.

Like ibritumomab, tositumomab is indicated only for patients who have less than 25% marrow involvement by lymphoma (documented by bilateral iliac biopsy). Unlike ibritumomab, tositumomab is administered according to a patient-specific whole-body radiation-absorbed dose calculated from imaging with ^{131}I-labeled antibody. The treatment schema, however, remains similar: Patients receive a 450-mg infusion of unlabeled tositumomab followed by 5 mCi of ^{131}I-labeled tositumomab for dosimetry. Serial imaging (carried out after administration and before voiding; between 2 and 4 days; and finally between 6 and 8 days after administration) allows calculation of the radiation-absorbed dose to the body [32–34]. This dosimetry step is necessary, given significant interperson variation in dehalogenation of the isotope from the antibody and significant urinary excretion, leading to variable clearance of the radioimmunoconjugate. A week later, the therapeutic dose is administered, again preceded by 450 mg of cold tositumomab antibody. The dose of ^{131}I-tositumomab is determined by the patient-specific dosimetry performed during the first phase, calculated to administer a total-body dose of 75 cGy.

Pharmacokinetics and dosimetry

Initial phase I and II studies determined the whole-body, radiation-absorbed dose to be 75 cGy for patients with adequate marrow reserve, as evidenced by marrow cellularity greater than 15% and a platelet count greater than 150,000/μL [35•,36,37]. Accordingly, a 450-mg infusion of unlabeled tositumomab is followed by an amount of ^{131}I-labeled tositumomab calculated to deliver no more than 75 cGy to the body.

Toxicity assessment of tumor dose response has been performed using patient-specific conjugate imaging and three-dimensional images with single-photon emission computed tomography (SPECT) and CT-based tumor volumes. In a study of 15 patients using detailed SPECT-based three-dimensional analysis, total-body tumor burden, individual lesion size, tumor-absorbed dose, and spatial absorption of dose were compared with response and time of tumor shrinkage. The SPECT-based doses were within 2% to 5% of the calculated dose by conventional methods. None of the absorbed dose estimates correlated with tumor response. The whole-body tumor burden had no impact on overall response and toxicity [38•]. A similar study in 52 patients suggests that combination of pretherapy conjugate views and intratherapy SPECT views for dosimetry calculation provides better correspondence between the average tumor dose and degree of response, although statistical significance was not reached [38•].

Phase I/II clinical trials

The initial safety and efficacy of ^{131}I-tositumomab was established in a phase I/II study of 59 patients for which an ORR of 71% was reported along with a CR rate of 34% [40]. Dose escalation to establish the maximally tolerated nonmyeloablative total-body dose (MT-TBD) was stratified by absence or presence of prior autologous stem cell transplant status, demonstrating an MT-TBD of 75 cGy and 45 cGy, respectively. The maximum tolerated dose for patients with platelet counts of 100,000 to 149,000 was 65 cGy. Of the 42 patients with relapsed or refractory, low-grade, or transformed NHL, an ORR of 83% with a CR rate of 48% was achieved.

Subsequently, a multicenter phase II study assessed the safety and efficacy of the nonmyeloablative dose of the tositumomab regimen specifically in relapsed or refractory, low-grade, and transformed NHL [41]. Forty-seven patients were enrolled and treated via patient-specific dosimetry calculations, demonstrating an ORR of 57% with a CR rate of 32%; the median duration of response was 9.9 months overall and 19.9 months for patients achieving a CR. This trial established the reproducibility and safety of the dosimetry calculations and the feasibility of administration in a multicenter setting. Interestingly, the ORR and CR rates were similar in patients with low-grade and transformed NHL (60% and 50%, respectively).

Phase III clinical trials

In the multicenter pivotal phase III study of approximately 60 patients with refractory or transformed low-grade B-cell NHL, 65% achieved objective responses (CR/PR) with ^{131}I-tositumomab, compared with 28% after their last qualifying chemotherapy. The median duration of response was 6.5 months with ^{131}I-tositumomab, compared with 3.4 months with their last qualifying chemotherapy [42•].

The interim analysis on the expanded-access trial bolsters these results. This expanded trial enrolled 475 patients with relapsed or refractory NHL in 65 academic and community centers. Of the 394 evaluable patients, an ORR of 59% with a median duration of 15 months was obtained, with the median duration of response not yet reached for the 26% of patients attaining a CR with 9 months of follow-up [43]. Responses can be durable, with a median duration of 4.8 years in the select group (28%) of patients attaining a CR across five trials (n=582) and a range from 3 months to 5.5 years [44].

A follow-up study in patients with multiple relapsed or refractory low-grade or transformed low-grade NHL reported a confirmed CR rate of 30%, and 70% of the treated patients who achieved a CR were in CR for up to 7.8 years. The overall CR rate in this study was 56%, with a median duration of response of 14.7 months [45].

Side effects and contraindications

The dose-limiting toxicity of tositumomab is mainly myelotoxicity. Adverse reactions related to infusion are minimal, compared with those seen with ibritumomab, and both agents show minimal nonhematologic toxicities. Because of release of ^{131}I, thyroid blockage is required for therapy with ^{131}I-tositumomab. Patient preparation with a saturated solution of potassium iodide or Lugol's iodine should be started 24 hours before therapy and continued for 14 days after the last dose of ^{131}I antibody. Subclinical hypothyroidism may occur, with a rise in thyroid-stimulating hormone (TSH). In some instances this may be caused by low titers of antimouse antibody causing falsely elevated values.

In a long-term follow-up study of 191 patients with low-grade and transformed low-grade NHL, increased TSH or initiation of thyroid medication was found in 7.1% and 12.8% of patients at 2 and 4 years, respectively [46]. The median time of HAMA positivity was 147 days in 13% of patients. Myelodysplasia and secondary cancers were seen in 2.2% of patients; however, the median number of chemotherapy treatments for the patients was four, and no significant difference was observed from patients treated with standard chemotherapy [46]. According to a 2003 report from ASCO, none of the 76 untreated patients who received ^{131}I-tositumomab as their initial treatment has developed myelodysplasia, with a median of 4.1 years of follow-up [47]. Although the numbers from this study are small, it suggests that a multihit pathogenesis for treatment-related myelodysplasia and leukemia is the likely culprit, with radiotherapy representing merely one component of the process.

In patients with no prior chemotherapy, the HAMA response can be as high as 65%, but it is less for those previously treated with chemotherapy, with a reported incidence of approximately 6% to 9% [42•,48]. When tositumomab is used in patients previously treated with fludarabine, the HAMA incidence is negligible [49].

Radiation safety

Due to gamma and beta emission, appropriate lead shielding is required during administration of the therapy dose. According to the guidelines of the US Nuclear Regulatory Commission, if the total effective dose of ^{131}I to another individual from exposure to a treated patient is less than 500 mrem, it can be administered as outpatient therapy. This means that treatment with ^{131}I-tositumomab can be given throughout the United States on an outpatient basis [50].

It is critical to educate the patient and family about appropriate radiation safety issues, particularly regarding the disposal of trash that may be contaminated with radioactivity. The patient and family must also be made aware that the gamma emissions of ^{131}I may cause radiation alarms to be set off. It may be prudent to provide the patient with a card stating the amount of radioactivity administered, the date of treatment, and the name and contact number of the responsible physician or radiation safety official.

High-dose therapy

Press *et al.* [51] evaluated a regimen of high-dose ^{131}I-tositumomab and peripheral blood stem cell transplantation in 25 patients. Their results showed an ORR of 86% and a CR rate of 79%. Thirty-nine percent of the patients survived free of recurrence for 5 to 10 years without any further therapy. The initial evaluation was extended to include 29 patients, who received therapeutic infusions of 10.4 to 29.0 gigabequerels (281–784 mCi) of ^{131}I-murine B1.

Further use of myeloablative doses along with stem cell transplantation and chemotherapy with etoposide and cyclophosphamide led to an overall survival rate of 83% and a progression-free survival rate of 68% with a median follow-up of 2 years [52].

Tositumomab has also been studied for high-dose therapy in patients with mantle cell lymphoma. In a pilot study with seven patients, the dose range was 261 to 495 mCi. Five of seven patients were in CR at 3 years [53]. In a study of 11 patients with relapsed or refractory mantle cell lymphoma, treatment included high-dose tositumomab, chemotherapy, and stem cell infusion. The overall survival rate was 93% at 3 years, and a 61% rate of progression-free survival was reported [54].

Whereas low-dose therapy offers palliation, high-dose therapy may provide prolonged relapse-free survival and the potential for prominent cure. Response rates, especially CRs, are significantly higher with high-dose myeloablative therapy than with low-dose therapy. Toxicity and treatment-related mortality are limited even in patients who have previously undergone myeloablative chemotherapy without and even with 12 Gy of total-body irradiation. Hypothyroidism is more significant, occurring in over 50% of patients. The toxicity of high-dose therapy is greater, with more incidence of hypothyroidism. Its dose-limiting toxicity is reversible cardiopulmonary disease (*ie*, radiation pneumonitis and cardiac dysfunction) with a dose greater than or equal to 27 cGy.

Alpha emitters have also been investigated for potential use in treatment of NHL. A preclinical study of rituximab labeled with ^{211}astatine suggests favorable use [55].

New Directions

In a phase III trial of tositumomab in previously untreated patients with low-grade or transformed NHL, 76 patients (94%) had an objective response, and 63% achieved CRs [56]. The role of radioimmunotherapy as an upfront strategy

is currently investigational, although long-term durable responses in relapsed and refractory patients are encouraging.

The Southwest Oncology Group conducted a phase II study in patients with untreated follicular lymphoma, evaluating six cycles of CHOP followed 4 to 8 weeks later by ^{131}I-tositumomab. The ORR for the entire regimen was 90%, comprised of 67% CRs and 23% PRs. Fifty-seven percent of patients who achieved less than a CR with the CHOP regimen improved further with the addition of radioimmunotherapy. The 2-year progression-free survival and overall survival rates are estimated at 81% and 97%, respectively [57].

Based on the responses in transformed disease, this concept of using adjuvant radioimmunotherapy after chemotherapy is being evaluated in high-risk untreated elderly patients with diffuse large B-cell lymphoma, treated with R-CHOP followed by ^{90}Y-ibritumomab tiuxetan. The role of radioimmunotherapy in diffuse large B-cell lymphoma and other histologies (*eg*, mantle cell lymphoma) is an area of intense clinical research.

Other Radioimmunotherapy Agents

An antibody against CD22 is under evaluation for treatment of NHL. This agent, LL2 (initially called EPB-2), was first studied in its murine form. A Fab' fragment labeled with ^{99m}technetium targeted NHL extremely well, with only normal spleen showing uptake of this antibody [58,59]. Later, this antibody was humanized, meaning that complementarity-determining regions were grafted onto the human framework region hLL2 (epratuzumab). The use of this antibody in NHL was studied with various labels, including ^{131}I, ^{90}Y, ^{186}rhenium, and ^{67}copper (^{67}Cu) [60–63]. Another radiolabeled antibody, Lym-1, which targets the HLA DR10b subunit expressed on malignant B cells (Oncolym; Peregrine, Tustin, CA), has been explored for use in NHL. ^{131}I- and ^{67}Cu-labeled forms have been investigated. In an initial trial of ^{131}I-Lym-1 in 30 patients, 57% had durable responses, including three CRs. ^{67}Cu allows imaging and has therapeutic (beta-emitting) effect. A favorable response was seen in seven of 12 patients (58%) with NHL [64,65].

CD19, a rapidly internalizing antibody that is universally expressed on B cells, has been used for targeting cells in leukemia. The experience in lymphoma is limited, and the targeting is probably suboptimal [66].

Anti-CD37 is also an internalizing antibody against antigen that is present more abundantly on B cells than on T cells. Its internalization is moderate and less than that of CD19. Two initial studies were not favorable for its use, compared with anti-CD20 antibodies [67,68].

Other Approaches

Multistep targeting approaches have been investigated in attempts to improve the therapeutic index of radioactivity. One approach uses the tumor-targeting specificity of an anti-CD20 streptavidin fusion protein (anti-CD20 SFv4/SA) that binds to low–molecular weight radioligand. It involves administration of a fusion protein consisting of the tumor antigen-binding construct fused with a molecule that can bind to radioligand with high affinity. Clinical trials with an anti-CD20/streptavidin fusion protein followed by a synthetic biotin galactose clearing agent to remove unbound protein and a radiotherapeutic effector, ^{90}Y/^{111}In-DOTA-biotin, have demonstrated significantly greater radiation delivered to tumor, with significantly reduced exposure to normal tissue leading to less dose-limiting myelosuppression [69].

Conclusions

The radioimmunotherapy agents ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab have established themselves as welcome and efficacious additions to the panoply of treatment options for indolent lymphomas. Currently, they are indicated for the treatment of relapsed and refractory indolent and transformed lymphomas, and the majority of patients will have failed either chemotherapy or rituximab treatment (or both) previously. The effectiveness of these agents in rituximab-refractory patients is therefore significant, given the overwhelming use of rituximab (alone and in combination) in the initial treatment strategies of both indolent and aggressive NHL.

The optimal timing of radioimmunotherapy in the treatment plan is an area that warrants significant investigation. Whether the more proximal use of radioimmunotherapy can bring more durable responses without significant long-term toxicity is yet to be determined. Several trials addressing this issue are currently in the design or early implementation stages, and their results will determine whether radioimmunotherapy has a role in front-line therapy for B-cell lymphomas. Particularly in patients with relatively aggressive tumors or bulky disease, combined ibritumomab–rituximab chemotherapy (CHOP-R-Z) regimens hold promise.

Which radioimmunoconjugate to use is currently a matter of significant debate. Direct comparisons in clinical trials are unlikely to occur, and for the time being the treating physician may make these decisions based on institutional availability, the physical properties of the isotopes, and the available clinical trials relevant to each scenario. Until more definite guidance can be given, *vive la difference*.

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