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Radioimmunotherapy based conditioning regimens for stem cell transplantation

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Abstract

Radioimmunotherapy (RIT) combines the mechanism of action and targeting capability of monoclonal antibodies with the tumoricidal effect of radiation and has shown promising results in the treatment of various hematologic malignancies. Based on RIT's efficacy and safety profile, many investigators have evaluated its use in transplant conditioning regimens with the goal of improving long-term disease control with limited toxicity. In lymphoma, two basic transplant approaches targeting CD20 have emerged: 1. Myeloablative doses of RIT with or without chemotherapy, and 2. Standard non-myeloablative doses of RIT combined with high-dose chemotherapy. Myeloablative RIT has been shown to be feasible and efficacious using escalated doses of I-131-Tositumomab (Bexxar), Y-90-ibritumomab tiuxetan (Zevalin), and I-131-rituximab with or without chemotherapy followed by autologous stem cell transplant (ASCT). The second approach predominantly has used standard doses of Y-90-ibritumomab tiuxetan or I-131 Tositumomab plus BEAM chemotherapy followed ASCT. RIT targeting CD-45, CD-33 and CD-66 prior to allogeneic transplantation has also been evaluated for the treatment of acute leukemia. Overall RIT-based transplant conditioning for lymphoma and leukemia has been shown to be safe, effective, and feasible with ongoing randomized trials currently underway to definitively establish its place in the treatment of hematologic malignancies.

Keywords

Radioimmunotherapy; stem cell transplantation; CD20; CD45; I-131; Y-90

Introduction

Despite advances in radiation therapy, chemotherapy, and standard radioimmunotherapy (RIT), the vast majority of patients with lymphoma are not cured by their primary therapy.^{1, 2} Once patients relapse after their primary therapy, they are even less likely to be cured with more standard approaches.^{3–5} For this reason a number of investigators have evaluated the use of high dose therapy and autologous stem cell transplantation with the hopes to improve progression free (PFS) and overall survival (OS) in patients with relapsed or high-risk initial disease. Randomized phase III trials have shown an improvement in PFS and OS when individuals with chemo-sensitive relapsed or high- risk lymphoma are treated with high dose

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therapy and autologous transplantation.^{6–8} Nevertheless, despite the use of intensified regimens with stem cell support, the majority of patients will still relapse. Furthermore a significant proportion of patients will never be considered for high dose approaches due to their chemoresistant status, advanced age or medical co-morbidities. Thus, novel conditioning regimens are required to improve remission durations, survival, and to allow a greater number of patients to be treated with this potentially curative approach.

Investigators and clinicians have long known that radiation is one of the most effective therapies for the treatment of hematologic malignancies including leukemia and lymphoma.^{9–11} For this reason investigators have incorporated total body irradiation into transplant conditioning regimens and have demonstrated its efficacy.^{12,13} In fact, studies demonstrated a distinctly inverse relationship of recurrence rates to radiation dosage. Fuks et al evaluated external beam radiation therapy in the treatment of malignant lymphoma and suggested that doses over 4,400Gy result in 6 % relapse rate within the radiation field as compared to 63% at the doses less than 2,750Gy¹⁴. The importance and the efficacy of escalated doses of radiation were confirmed in a randomized phase III trial comparing 12Gy total body irradiation (TBI) versus 15.75Gy (TBI). This study of AML patients in first remission illustrated that the higher radiation dose resulted in a lower relapse rate but likewise yielded a higher treatment related mortality such that the overall survival was equivalent in both groups.¹⁵ Nevertheless, investigators hypothesized that if the radiation dose could be safely escalated to tumor sites, relapse rates would be reduced without incurring additional toxicity. Thus the concept of radioimmunotherapy and high dose radioimmunotherapy prior to transplantation was born.

Radioimmunotherapy-based transplants for lymphoma

Antibody isotope conjugates used prior to transplantation for NHL

As it has been outlined in other sections of this issue, a variety of radioimmunoconjugates have been employed for the treatment of NHL. Most investigators have utilized CD-20 as a target for radioimmunotherapy based on its predictable expression on 80% of B-cell lymphomas, its lack of significant shedding, its infrequent internalization, and its rare modulation.^{16,17} Even though most groups have used CD-20 as a target, a variety of isotopes have been utilized for this approach, including I-131, Yttrium 90 and Rhenium 186.^{18–25} Table 1 summarizes a selection of radioimmunoconjugates that have been studied as part of stem cell transplant conditioning regimens for lymphomas.

Clinical strategies of radioimmunotherapy based transplants for NHL

Two basic strategies have emerged for the use of radioimmunotherapy as part of conditioning regimens. The first approach emphasizes the efficacy of the radiolabeled antibody by escalating the dose of the RIT and giving this either with or without high dose chemotherapy. Potential advantages of the escalated radioimmunotherapy regimen include delivering potentially curative doses of radiation therapy to all disease sites that may overcome chemoresistance. Limitations include technical aspects of dealing with very high doses of radioisotopes as well as specific dosimetry issues. The second method utilizes standard non-myeloablative radioimmunotherapy combined with myeloablative chemotherapy. Advantages of this treatment design primarily include ease of administration and the potential to escalate therapy above full chemotherapy-based conditioning regimens whereas disadvantages primarily center around the relatively low dose of radiation that is delivered to tumor sites. Each of these two strategies will be summarized below.

High dose radioimmunotherapy (HD-RIT) with or without chemotherapy followed by autologous stem cell transplantation (ASCT)

High-dose I-131-based approaches—The first group to employ the strategy of dose escalation using a radioimmunoconjugate followed by autologous stem cell transplantation (ASCT) was the Seattle Consortium led by Dr. Oliver Press. These studies evaluated escalating doses of I-131 anti B-cell antibodies and demonstrated the importance of individualized organ-specific dosimetry when escalated radiation doses were utilized due to the variability of absorbed radiation doses to non-target organs. The initial Phase I trials established the maximally tolerated dose (MTD) of single agent I-131 tositumomab followed by ASCT to be 27 Gy to the critical normal organ receiving the greatest radiation.¹⁸ In most circumstances, the critical normal organ receiving the highest absorbed radiation dose was the lung with doses in excess of 27 Gy resulting in higher rates of cardiopulmonary toxicity.¹⁸ This strategy demonstrated that, on average, tumor sites would receive approximately 10 times the radiation dose as would the whole body and twice the radiation dose as would the critical organs such as the lungs. Not surprisingly, due to the targeted nature of this therapy, the non-hematopoietic toxicities associated with single agent high dose radioimmunotherapy were very low.¹⁸ Most importantly, overall and complete responses rate were 95% and 84%. These initial studies also demonstrated the predicted dose-response relationship with patients that received on average 20Gy to the highest critical normal organ enjoying improved PFS as compared to those that received lower doses of therapy (Figure 1).²⁶ The relative long-term efficacy of this high-dose RIT strategy was evaluated via a multivariable cohort analysis of 125 patients with relapsed or refractory follicular lymphoma treated with either myeloablative I-131 tositumomab followed by ASCT or conventional high dose therapy followed by ASCT. In this study, the estimated 5-year OS for high-dose RIT was 67% and for conventional high-dose therapy was 53% ($p=.004$).²⁷ Likewise, 5-year PFS was 48% for the high-dose RIT group and 29% for the conventional transplant group ($p=.03$) (Figure 2).²⁷ Furthermore, 100-day treatment-related mortality was lower in the HD-RIT group than C-HDT group (3.7% versus 11.2%) with no evidence of increased MDS/AML at 8 years of follow-up.²⁷ Based on the exceedingly low non-hematopoietic toxicity of single-agent HD-RIT followed by ASCT, we recently evaluated this strategy in older adults with relapsed B-NHL. Older patients with refractory or relapsed NHL typically have limited therapeutic options largely due to the excessive toxicity associated with potentially curative dose intense regimens and co-morbidities.^{28,29} In this study, 24 patients ≥ 60 years of age with relapsed or refractory B-NHL received high-dose RIT targeted to ≤ 25 –27Gy to normal organs followed by ASCT.²⁸ Notable findings from this series included low rates of non-hematopoietic toxicity ($<10\%$ grade 4), no treatment-related deaths, and an estimated 51% 3yr PFS.²⁸

Building on this strategy, the group in Seattle investigated the feasibility of adding high dose chemotherapy to the high dose radiolabeled antibody regimen. In a phase I/II study, the maximally tolerated dose of I-131 tositumomab that could be safely combined with 60mg per kg of etoposide and 100mg per kg of cyclophosphamide followed by ASCT was 25 Gy to the highest critical normal organ.³⁰ Again the dose limiting toxicity was cardiopulmonary, however, when combined with high-dose chemotherapy, other typical transplant related toxicities such as mucositis did occur. Importantly, non-randomized controls treated with identical doses of chemotherapy but with total body irradiation had inferior PFS ($p<0.002$) and OS ($p<0.004$) compared to those who received radiolabeled antibody based regimen.³⁰ More recently, we reported a subset of 16 patients with refractory mantle cell lymphoma who had been treated with this approach. 3-year PFS and OS from transplantation were estimated at 61% and 93%, respectively.³¹ Extended phase II studies using this combined high-dose chemoimmunotherapy regimen in various B-NHL histologies are ongoing to better define the safety and efficacy of this regimen.

Other groups have also utilized myeloablative doses of I-131 conjugated antibodies. Dr. Behr and colleagues published a series of seven patients with relapsed NHL treated with high dose I-131 labeled Rituximab following the same dosimetry as the Seattle group to deliver 25 Gy to the highest normal organ; their data also suggested that this approach is effective with minimal toxicity³².

High-dose Y-90 based approaches—Other investigators have evaluated the use of escalating the dose of Y-90 ibritumomab tiuxetan (Zevalin®) in combination with chemotherapy and autologous stem cell transplantation. Dr. Winter and colleagues escalated the dose of Zevalin beyond 0.5 mCi/kg along with high dose BCNU, etoposide, cytarabine, melphalan (BEAM) and ASCT and found the 3-year PFS and OS to be 43% and 63%, respectively in a heavily pretreated group of 33 patients with relapsed and refractory lymphoma³³. Twelve out of the thirty-three patients safely received a dose ≥ 0.5 mCi/Kg and the most common toxicities were similar to that seen with BEAM/ASCT. In an updated report, this group demonstrated that Zevalin doses calculated to deliver up to 1500 cGy to critical organs (liver in most cases) can be safely combined with high-dose BEAM and ASCT in the study of 44 patients with relapsed and refractory NHL.³⁴ The updated three year overall and progression-free survivals were 52% and 37%, respectively. Flinn, et al conducted a dose finding trial of Zevalin with four dose cohorts (0.4 mCi/kg; 14–18 Gy, 24 Gy or 28 Gy to the liver)³⁵. All patients had rapid engraftment with no significant hepatotoxicity despite the fact that the liver was the non-target site that received the highest absorbed dose of radiation. Non-hematopoietic maximal tolerated dose (MTD) has not been reached and dose escalation continues.

The group at the City of Hope studied 31 patients with poor-risk or relapsed non-Hodgkin lymphoma who received high-dose Zevalin and high-dose etoposide (60mg/kg) and cyclophosphamide (100 mg/kg) followed by ASCT. Zevalin was dosed to deliver 10Gy to highest normal organ and capped at 100mCi of Y-90. At a median follow-up of 22 months, the group reported an encouraging 2-year relapse-free and overall survival of 78% and 92%, respectively with efficacy across various B-NHL histologies (figure 3) and toxicities comparable to standard TBI-based regimens.³⁶ In contrast to the City of Hope dosing regimen, Vanazzi and colleagues reported their data using a mCi/kg dose escalation of Y-90-Ibritumomab tiuxetan followed by ASCT.³⁷ This study treated patients at dose levels of .8, 1.2, and 1.5 mCi/kg 13 days prior to ASCT. The median Y-90 dose in this heavily pre-treated group of 18 elderly patients was 90mCi and the maximal estimated radiation exposure to liver was 30Gy, yet reported toxicity rates were no higher than standard transplant regimens.

Standard RIT plus high dose chemotherapy and ASCT

An alternative strategy to myeloablative RIT is to add standard outpatient doses of RIT to full dose myeloablative chemotherapy allowing for further intensification of a maximal chemotherapeutic regimen. This approach was evaluated in a phase I trial by Dr. Vose and colleagues in 23 patients with relapsed or refractory B-cell NHL who were treated with escalating doses of standard I-131 tositumomab (Bexxar) up to 0.75Gy plus high-dose BEAM followed by autologous stem cell transplantation (ASCT).³⁸ This study demonstrated that the full 0.75Gy whole body dose of Bexxar could be safely administered 7 days prior to initiating full dose BEAM chemotherapy and 14 days prior to ASCT with no appreciable increase in toxicities. This regimen also achieved a CR rate of 57% and event free survival (EFS) of 39% at a median follow-up of 38 months in a group of heavily pre-treated patients.³⁸ A follow up phase II study of 40 chemosensitive diffuse large B-cell lymphoma patients by the Nebraska group confirmed the feasibility of this regimen and yielded an estimated 3-year PFS of 70% and OS of 81%.³⁹ These encouraging preliminary data have led to an ongoing phase III trial comparing Bexxar-BEAM to Rituximab-BEAM in patients with relapsed, chemosensitive

diffuse large B-cell lymphoma. Similarly, the City of Hope group reported their experience in patients with relapsed and refractory NHL treated with standard Y-90-ibritumomab tiuxetan (Zevalin) followed by full dose BEAM chemotherapy and ASCT.⁴⁰ In this study of 33 predominantly older patients, these investigators were able to administer the standard 0.4mCi/kg dose of Y-90 14 days prior to ASCT and 7 days prior to initiating the BEAM regimen without incurring any obvious added toxicities. A favorable 2 year OS (88% versus 65%) and PFS (72% versus 67%) were noted in the Zevalin-BEAM group as compared to patients receiving standard BEAM alone. Overall, the findings from the Nebraska and City of Hope groups as well as others suggest that standard doses of either I-131-tositumomab or Y-90-ibritumomab tiuxetan can be safely administered prior to full dose BEAM and ASCT. Ongoing randomized trials will need to be completed to ascertain the relative benefit of these intensified, targeted regimens

RIT based Allografting for NHL

Though the results with radiolabeled antibody based conditioning regimens appear encouraging, unfortunately not all patients achieve prolonged remissions. Furthermore, many patients are unable to undergo any high dose therapy due to inability to collect peripheral blood stem cells, extensive prior therapy, advanced age, or multiple comorbidities. For such patients, non-myeloablative allogeneic transplantation has been employed with the hopes to induce a graft versus lymphoma (GVL) effect and achieve long-term remissions. In fact, preliminary data from many studies have suggested that this is possible, but inferior outcomes are associated with chemo-resistance, bulky disease, aggressive histology or rapidly progressive lymphoma.^{41–46} It is in this setting that additional safe and effective cytoreduction is needed to improve outcomes of non-ablative transplantation. It has been hypothesized that RIT could provide the cytoreduction to safely induce disease control with minimal non-hematologic toxicity and the allogeneic transplant could maintain the remissions via the GVL effect as well as reconstitute hematopoiesis. Early studies utilizing this approach have been performed both at our center and elsewhere.^{47,48} We recently reported our data using 0.4 mCi/kg Y-90 ibritumomab tiuxetan followed by fludarabine and 2Gy TBI and matched allogeneic transplantation⁴⁹ (Figure 4). Sixteen patients with relapsed or refractory CD20+ NHL or chronic lymphocytic leukemia (CLL) and evaluable disease, who had too high-risk lymphoma (94% chemoresistant) for a routine non-ablative transplant and were not eligible for a traditional myeloablative transplant due to advanced age, co-morbidities, or prior therapy were treated this regimen. We found that adding RIT did not result in unexpected non-hematopoietic toxicity. Importantly, 7 of 16 patients demonstrated responses by day 28 after transplant suggesting the potential efficacy of the RIT even in chemoresistant disease. The accrual to this trial and long term follow up of these patients continues. Other groups have also reported preliminary data using RIT prior to allogeneic transplantation for NHL^{48,50} Dr. Khouri and colleagues reported the use of escalating doses (.2, .3, .4mCi/kg) of Y-90 ibritumomab tiuxetan prior to cyclophosphamide, fludarabine, rituximab, and allogeneic transplantation in 7 patients with relapsed B-NHL/CLL suggesting that this approach was safe and feasible.⁵⁰ In total, the preliminary data suggest that the addition of RIT to reduced intensity allogeneic transplantation is safe and feasible, though longer follow up will be required to determine if the addition of these agents results in improved long-term disease-free survival.

Radioimmunotherapy-based transplants for leukemia

Leukemias have also long been known to be highly sensitive to radiation therapy.⁵¹ In part for this reason, TBI has been employed as part of transplant conditioning regimens to maximize the anti-leukemic effect.¹⁵ Likewise, investigators have sought to intensify the dose to hematopoietic sites in such patients to increase response rates and reduce post transplant relapse. A variety of radioimmunoconjugates have been employed for this purpose (Table 2) and two basic strategies have emerged. The first approach that was investigated included the

addition of RIT to full dose preparative regimens either with or without TBI. Early studies utilizing the myeloid antigen CD33 demonstrated that marrow and spleen could be preferentially targeted in most patients, though it was noted that the residence time of I-131 in some patients rendered a lower radiation exposure to hematolymphoid organs than to non-target sites.⁵² It was hypothesized that this short residence time could be attributed to the internalizing properties of the CD33 antigen and the observation that internalized I-131-conjugates were rapidly dehalogenated resulting in release of the isotope from the cell.⁵³ In an attempt to overcome this limitation, investigators focused on the non-internalizing antigen, CD45. CD45 is expressed on the majority of hematopoietic cells, approximately 90% of acute leukemias, and not known to be expressed on non-hematopoietic tissues.^{54,55} Initial studies by the Seattle group indicated that the use of this strategy could deliver a median of 24Gy and 50Gy of additional radiation to marrow and spleen, respectively, along with 120mg/kg CY and 12Gy TBI.⁵⁶ More recently, a phase II study evaluated the use of this regimen along with 16mg/kg Bu and 120mg/kg CY for high-risk AML patients in first remission.⁵⁷ These data demonstrated that mean of 11.3 Gy and 29.7 Gy of additional radiation could safely be delivered to the marrow and spleen without an increase in non-relapse mortality and an estimated 61% 3 year DFS.

The second RIT transplant strategy that has been utilized for the treatment of leukemia is to add intensified radiation to reduced intensity preparative regimens allowing the majority of the targeted therapy to be maximally intensified. Preliminary results of this strategy were reported by Pagel and colleagues adding escalating doses of I-131 anti-CD45 therapy to the fludarabine/2Gy TBI regimen developed by Storb and colleagues.^{58,59} Thus far an additional 24Gy can be delivered to liver resulting in up to an added 46Gy to marrow and 81Gy to spleen without incurring an increase in early mortality. Dose escalation of this study continues. A second group also followed this strategy by combining either Y-90 or Re-188 labeled anti-CD66 antibodies followed by the reduced intensity regimen of fludarabine, ATG +/- Melphalan.⁶⁰ This study illustrated that a median of 21.9 Gy could be delivered to the marrow space and improved marrow delivery was noted with Y-90 over Re-188. Importantly, treatment-related mortality (TRM) was not observed to be higher than historical controls and overall survival at 2 years was 52%.

Future directions in RIT-based transplant conditioning regimens

Efficacious and minimally toxic, radioimmunotherapy has been rapidly evolving with encouraging results as part of the conditioning regimens for stem cell transplantation for lymphomas and leukemias. Numerous studies, including phase III trials, are ongoing to evaluate this approach in various clinical settings and showing promising results. There are, however, still many challenges and questions that need to be addressed including improving outcomes in patients with bulky, rapidly progressive disease and aggressive histologies.⁶¹ Development of new isotopes may hold the potential to further advance treatment outcomes. ⁶⁷Cu-labelled antibodies have been shown to yield higher and more persistent tumor uptake than their radioiodinated counterparts due to accumulation of labeled metabolites in tumor cells.⁶² Preclinical and clinic data suggest that efficacy and tolerability of RIT could also be further improved by escalating radiation delivered to the selected tumor sites via pre-targeting methodologies and extracorporeal immunoabsorption.^{63–66} Furthermore, exploration of new antibody-antigen combinations may also result in improved therapeutic indices for patients with NHL.⁶⁷ We anticipate that the ongoing clinical trials and innovative strategies will continue to establish the place of RIT in transplant regimens for lymphoma and leukemia.

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Figure 1. Progression-free survival of NHL patients treated with high-dose RIT and ASCT stratified by dose critical normal organs. (Adapted from Press et al, Lancet, 1995)

Figure 2. Overall survival (A) and progression-free survival (B) of patients treated either with HD-RIT using ^{131}I -tositumomab and ASCT or C-HDT and ASCT (Gopal AK et al, Blood 2003; 102(7):2351–2357)

Figure 3. Disease-free survival of 31 patients who underwent high-dose Y-90 ibritumomab tiuxetan and ASCT in NHL, based on histology (from Nademanee, A. et al. Blood 2005; 106:2896–2902)

Figure 4.

Schema of yttrium 90 (Y-90)/anti-CD20 RIT conditioning. CSP indicates cyclosporine; MMF, mycophenolate mofetil; PBSC, allogeneic peripheral blood stem cell transplantation; TBI, total body irradiation. (Gopal AK et al, Biol Blood Marrow Transplant 2006; 12(7): 697–702)

Table 1
Selected radioimmunoconjugates as part of autologous stem cell transplant conditioning regimens for lymphomas

Author (Year)	Isotope	Drug/Target	Lymphoma type/Setting	No. of patients	Outcomes
Press (1993) ⁶⁸	I-131	MB1/CD37 Tositumomab/CD201F5/CD20	B-NHL/Relapsed	19	95% (84 % CR)
Bierman (1993) ²⁴	Y-90	antiferritin/ferritin	Hodgkin's disease/Poor prognosis	14	21% (7 % CR)
Behr (2002) ²²	I-131	Rituximab/CD20	Indolent NHL/Relapsed	7	100% (86% CR)
Herpst (1995) ²³	Y-90	antiferritin/ferritin	Hodgkin's disease/Relapsed	39	51% (0% CR)
Knop (2004) ²⁵	Rh-186	Rituximab/CD20	B-NHL/Relapsed or Refractory	4	50% (25% CR)
Nademanee (2005) ³⁶	Y-90	Ibritumomab/CD20	B-NHL	31	2-year estimated RFS 78%
Winter (2005) ³³	Y-90	Ibritumomab/CD20	B-NHL/Relapsed or Refractory	33	3-year PFS 43%
Vose (2005) ³⁸	I-131	Tositumomab/CD20	B-NHL/Relapsed or Refractory	23	65% (57% CR)
Winter (2006) ³⁴	Y-90	Ibritumomab/CD20	B-NHL/Relapsed or Refractory	44	3-year PFS 52%
Finn (2006) ³⁵	Y-90	Ibritumomab/CD20	B-NHL/Relapsed or Refractory	16	80% (62.5% CR)
Krishnan (2006) ⁴⁰	Y-90	Ibritumomab/CD20	B-NHL	33	2-year PFS 88%
Vose (2007) ³⁹	I-131	Tositumomab/CD20	chemosensitive DLBCL	40	3-year PFS 70%
Gopal (2007) ²⁸	I-131	Tositumomab/CD20	B-NHL/Relapsed, > 60 years old	24	3-year estimated PFS 51%
Shimoni (2007) ⁶⁹	Y-90	Ibritumomab/CD20	NHL/Refractory	21	95% (52% CR) 2-year estimated PFS 52%

B-NHL= B cell Non-Hodgkin's Lymphoma; DLBCL= diffuse large B cell lymphoma; CR= complete response; PFS= progression free survival; RFS= relapse free survival; I-131= iodine-131; Y-90=Yttrium-90; Re-186= rhenium-186

Table 2
Selected trials utilizing RIT preparative regimens prior to allogeneic transplantation for AML

Author (Year)	Isotope	Target	Additional therapy	Leukemia type/Setting	No. of patients	Outcome
Appelbaum(1992) ⁵²	I-131	CD33	Cy/TBI	AML	4	75% CR
Jureic (1995) ⁷⁰	I-131	CD33	Bu/Cy	AML	19	95%CR, 53% TRM
Mathews (1999) ⁵⁶	I-131	CD45	Cy/TBI	AML/MDS/ALL	34	65mo DFS (AML)
Bunjes (2001) ⁷¹	Re-188	CD66	CY/TBI or Bu/Cy	AML/MDS	36	45% DFS at 18mo
Burke (2003) ⁷²	I-131	CD33	Bu/Cy	AML/CML/MDS	31	Median OS=4.9mo
Pagel (2005) ⁵⁸	I-131	CD45	Flu, TBI (2Gy)	AML/AML	33	55% DFS at 10mo
Rinehoffer (2005) ⁶⁰	Re-188/Y-90	CD66	Flu/ATG +/- Mel	AML/MDS	20	52% 2 yr OS
Pagel(2006) ⁵⁷	I-131	CD45	Bu/CY	AML- CR1	46	61% DFS at 3 yrs

AML= acute myeloid leukemia; MDS= myelodysplastic syndrome; ALL= acute lymphocytic leukemia; CML= chronic myeloid leukemia; CR = complete response; DFS= disease free survival; OS= overall survival; TRM= treatment related mortality; Bu= Busulfan; Cy= cyclophosphamide; Flu= fludarabine; ATG= Anti-thymocyte globulin; Mel= melphalan; TBI= total body irradiation; Gy= gray;I-131= iodine-131; Y-90= Yttrium-90; Re-188= rhenium-188