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Monoclonal Antibodies in Lymphoma –the First Decade

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INTRODUCTION

In the past decade, overall survival improvements have been observed in the two most common lymphoma histologies: diffuse large B cell lymphoma and follicular lymphoma. In follicular lymphoma, at least four independent datasets have confirmed these survival improvements. The monoclonal antibody rituximab has significantly contributed to these improved therapeutic outcomes. This issue will explore the impact of monoclonal antibody therapy on outcome in indolent lymphoma, and detail how this improved outcome has changed our practice. Furthermore, the role of monoclonal antibodies in maintenance regimens and the main indications for radiolabelled antibodies will be discussed in detail. Finally, possible future developments in the field will also be proposed, including the use of monoclonal antibodies in ablative transplantation, and in the treatment of leukemias.

November 1997 marked the dawn of a new era in cancer therapy with the United States Food and Drug Administration approval of rituximab – a monoclonal antibody targeting the CD 20 molecule on B lymphocytes. The initial indication was for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, non-Hodgkin's lymphoma (NHL). Subsequent indications have expanded to include first-line treatment of follicular, CD20- positive, B-cell NHL in combination with cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; treatment of low-grade, CD20-positive, B-cell NHL in patients with stable disease or who achieve a partial or complete response following first-line treatment with CVP chemotherapy; and for the first-line treatment of diffuse large B-cell, CD20-positive, NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens. Subsequent antibodies to reach the market for lymphoma include the radiolabeled anti-CD 20 antibodies iodine- 131 tositumomab and ibritumomab tiuxetan – each indicated for the treatment of relapsed or refractory low grade or follicular lymphoma, including transformed lymphoma and rituximab-refractory lymphoma. Alemtuzumab effectively targets CD52 in chronic lymphocytic leukemia, but has little clinical value in lymphoma. Other antibody strategies for leukemia are discussed by Dr. Mulford elsewhere in this issue. Denileukin diftitox, although not a classic antibody, represents another effective targeted immunotoxin- albeit limited to CD25 expressing cutaneous T-cell lymphomas. With one dominant antibody and four less utilized agents, what has been the measured impact on the outcome of lymphoma patients?

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Population studies measuring impact of monoclonal antibodies on follicular lymphoma survival

Measuring the survival impact of any therapy in a chronic disease such as follicular lymphoma (FL) is challenging and not well addressed by phase II or even moderately large phase III studies. Although previous series had cast doubt on the ability of therapy to impact survival in the indolent lymphomas, four recent studies looking at historical series of FL patients each concluded that survival in this disease is improving (table 1). The first was an analysis of the National SEER database looking at FL patients diagnosed from 1978–1999[1]. With nearly 15,000 patients in the data set, median overall survival (OS) for patients diagnosed 1993–99 (95 months) was superior to those diagnosed 1986–1992 (87 months), which was superior to those diagnosed 1978–1985 (82 months). The magnitude of the improvement was not great and represented a new finding perhaps in part because of the large numbers of patients utilized to uncover small differences, in part because of expanded management options, and in part because the analysis was restricted to patients with FL. For analyses requiring stratification by stage of disease, 12,088 patients were studied. Kaplan-Meier survival curves for two diagnosis eras (1983–1989 and 1990–1999) revealed a statistically significant 9-month increase (10.7 percent) in observed median survival. Among patients with advanced stage disease, median survival improved (63 months vs. 72 months) between the eras whereas in patients with limited/regional disease an observed median survival of 114 months was seen in each era. Survival improved across diagnosis eras for males, females, older and younger patients, and for all grades. Survival was similar for black and white patients in the early era and improved significantly across eras for white patients, but not for black patients. Of note, the rate of improvement for FL patients as a whole was relatively stable across the study eras and the authors concluded the effect was independent of any impact from monoclonal antibodies.

A second study supportive of the new paradigm and more strongly implicating the role of monoclonal antibodies was a retrospective look at a series of Southwest Oncology Group (SWOG) trials in patients with advanced stage FL[2]. With long term follow-up the 4 year overall survival (OS) rate in the most recent prospective clinical trials utilizing initial therapy with CHOP plus monoclonal antibodies (91%) was superior to similar trials utilizing a second generation anthracycline combination (79%) which was superior to the studies utilizing CHOP (69%). The authors concluded that initial choice of therapy may impact overall survival in advanced stage FL. In this report, the outcome of the most recent era was significantly better than had ever been observed historically.

In a third observation along this theme, five sequential studies from MD Anderson involving 580 subjects with stage IV FL treated 1972–2002 were analyzed for failure-free (FFS) and OS[3]. Five year OS rates improved chronologically from 64% to 95% across these trials and the authors even commented on a possibly observed plateau on the FFS curve. Finally, the Gruppo Italiano Studio Linfomi (GISL) recently reported on a series of phase II studies organized into four cohorts of front-line therapy with second generation anthracycline combinations including bleomycin, epidoxorubicin, cyclophosphamide, vincristine, prednisone and rituximab (BACOP/FR) given serially from 1988–2004. Four year OS rates ranged from 76% in the early studies to 97% with the most recent BACOP/FR cohort. They also observed a survival improvement in relapsed patients treated with rituximab plus chemotherapy when compared with chemotherapy alone[4].

In aggregate, the authors of these four reports conclude that newer treatment options result in better overall survival in patients with FL, yet none claim to identify specifically which treatment or when administered is important. At least three of these reports hint strongly that the first decade of monoclonal antibodies have impacted the survival of patients with FL.

Prospective controlled studies measuring impact of monoclonal antibodies on low grade lymphoma survival

Several recent randomized studies suggest a survival advantage with the early addition of rituximab to a chemotherapy regimen. The first to demonstrate this advantage was the German Low-Grade Lymphoma Study Group in their study of 428 patients with untreated advanced stage FL grades 1 and 2 randomly assigned to induction therapy with CHOP with or without concurrent rituximab[5]. With short follow-up, estimated probability of 95% vs 90% survival at two years significantly favored the rituximab containing cohort. Subsequent studies have demonstrated similar improvements in overall survival when rituximab is added to induction with the regimens CVP[6]; cyclophosphamide, doxorubicin, etoposide, prednisone and interferon (CHVP-I)[7]; mitoxantrone, chlorambucil, and prednisolone (MCP)[8]; and fludarabine cyclophosphamide and mitoxantrone (FCM)[9]. A systematic review and meta-analysis of rituximab added to chemotherapy in patients with indolent or mantle cell lymphomas analyzed patients previously treated and ultimately concluded that rituximab with chemotherapy is superior to chemotherapy in regards to overall survival[10]. There are no survival endpoints in the published prospective studies with radiolabeled antibodies, alemtuzumab or denileukin diftitox in lymphoma and their low utilization rate precludes retrospective registry analyses.

Prospective controlled studies measuring impact of monoclonal antibodies on aggressive lymphoma survival

The impact of antibodies on survival of patients with aggressive lymphomas such as diffuse large B cell lymphoma (DLBCL) will be easier to measure given the shorter natural history of the disease, but large registry-based analyses have not yet materialized because the use of rituximab with anthracycline based chemotherapies in this setting was uncommon before 2001. The first phase III published report demonstrating a 13% improvement in overall survival (OS) in elderly (>60 years) patients with DLBCL treated with R-CHOP compared to CHOP alone was presented at a national meeting in December 2000 followed by a published report in January 2002[11,12]. In March 2001, the British Columbia Cancer Agency recommended R-CHOP as preferred therapy for all newly diagnosed patients with advanced stage DLBCL in the province. A population-based retrospective analysis of this new treatment strategy demonstrated that among adult patients of all ages with DLBCL who received anthracycline based therapy, the 2 year OS estimate increased from 52% to 78% in the post-rituximab era[13]. These studies are discussed in detail in the article by Dr. Kahl.

Has practice been affected by the availability of monoclonal antibodies?

Based upon the aforementioned clear survival data, an anthracycline based chemotherapy regimen in combination with rituximab is the standard therapy for patients with newly diagnosed aggressive lymphomas. However, there remains no standard upfront therapy for patients with follicular lymphoma. Options for initial management of follicular lymphoma include observation until symptoms emerge, radiation therapy to limited sites of bulk disease, rituximab, and single agent or combination chemotherapy in combination with rituximab. Similar to large cell lymphoma, data suggests that when chemotherapy is given as therapy for follicular lymphoma, there is an advantage in progression-free survival, and possibly overall survival, when rituximab is combined with chemotherapy.

The NCCN non-Hodgkin's lymphoma database collects demographic, staging, treatment and outcome information on consecutive pts with NHL seen at 5 geographically diverse NCCN institutions (Dana-Farber, Roswell Park, City of Hope, Fox Chase and MD Anderson).[14] As expected, an analysis of this database between 7/2000 and 5/2004 revealed that the vast majority of patients with diffuse large B cell lymphoma received rituximab as part of their

initial therapeutic regimen. The only significant predictor of rituximab use was year of presentation (P<0.01), (adjusting for IPI, age, 1st line therapy, comorbidity, and center): after 7/01, 93% of pts received R compared with 69% prior to 7/01, in keeping with the evolution of published data during that time. During this same era, 52% of patients with follicular lymphoma received rituximab (either alone or with chemotherapy) and 25% received no therapy ("observation"). Unlike diffuse large cell lymphoma, the specific NCCN center was a significant predictor of rituximab use; rates of rituximab use in follicular lymphoma varied from 7% to 84% within these 5 centers during this period. Additionally, the overall approach to follicular lymphoma clearly evolved over this relatively short era: as of 7/01, significantly fewer pts were observed (21%) as compared to pre- 7/01 (36%).

The National LymphoCare study is a large community-based, prospective observational study of newly diagnosed FL patients designed to collect data on representative patterns of clinical presentation, management, and outcome. This study enrolls patients from over 200 centers in the United States, and the vast majority of patients are enrolled from community-based practice settings. Over 2500 patients have been enrolled in this study, and preliminary demographic results suggest this population is similar to that of the SEER registry. As expected, initial therapeutic regimen varied depending upon patient and physician factors. Almost 20% of patients were initially observed. Of patients treated, over 80% received rituximab, either as a single agent, or in combination with chemotherapy. The most commonly utilized chemotherapy-rituximab combination was the R-CHOP. Of patients initially observed, the most commonly utilized regimen following observation was single agent rituximab[15].

Based upon these two prospective databases, it is clear that the approach to follicular lymphoma has evolved to incorporate rituximab early in the course of therapy. Indeed, one study in 2003 suggested that 75% of rituximab administrations were for indications outside of the FDA-approved label.[16] Observation continues to be practiced, but there is evidence that single agent rituximab may be replacing observation in many centers. With longer follow-up of this therapeutic approach, it is hoped that impact on survival and other important endpoints may be observed in these databases.

Other monoclonal antibodies

Unlike the situation of rituximab, radioimmunotherapy (ibritumomab tiuxetan and iodine-131 tositumomab) and alemtuzumab have not been routinely incorporated into therapy for most patients. The reasons for this are multifactorial, and discussed in detail elsewhere.[17] Alemtuzumab is discussed in detail in the chapter by Dr. Lin on chronic lymphocytic leukemia. Studies evaluating these agents as upfront therapy in the treatment of common lymphomas are underway. Radioimmunotherapy is the subject of two other chapters in this issue, by Dr. Schaefer-Cutillo and myself and by Drs Zhang and Gopal.

Conclusions and Future Directions

Practice in the United States has evolved to incorporate rituximab as part of initial therapy of both follicular and diffuse large B cell lymphoma. Several studies suggest that largely due to the use of this agent, overall survival has improved for both of these common lymphoma subtypes. The role of rituximab maintenance regimens is the subject of another chapter in this issue by Drs Moccia and Ghielmini. Additionally, should therapeutic vaccinations become available as a treatment option for patients with follicular lymphoma, it will be critical to again evaluate the optimal timing of rituximab when incorporated into that therapeutic approach, as discussed by Drs LaCasce and Freedman in this issue. Finally, as mentioned in Dr. Leonard's paper in this issue, several novel monoclonal antibodies, including humanized antibodies directed against CD20, are under development. In order for these antibodies to replace or add

to rituximab, carefully controlled clinical trials designed to measure the critical endpoints-progression-free survival and overall survival-will be required. As we enter the second decade of the monoclonal antibody therapeutic era, we expect that the significant improvements in patient outcome will continue.

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Table 1

Reports Demonstrating Improved Survival in Follicular Lymphoma

Patient Source Years	# Pts	Magnitude of improvement	Comments	Ref
SEER	14,637	Median OS 82 to 95 months	Consistent improvement across years	1
1978 – 1999			Improvement predates monoclonal antibodies	
SWOG	960	4 year OS 69 to 91%	ProMACE survival superior to CHOP	2
1974 – 2000			CHOP + Moab survival superior to others	
MDACC	580	5 year OS 64 to 95%	Improved salvage options contributed	3
1972 – 2002			Authors hint at trend toward FFS plateau	
GISL	580	4 year OS 76 to 97%	Rituximab significant after adjusted for FLIPI	4
1988–2004			Frontline and salvage options contributed	