5 Minute JournalClub

Key ASH Presentations
Issue 9, 2012

Radioimmunotherapy for FL

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Develop evidence-based treatment algorithms for patients presenting with high tumor mass follicular lymphoma (FL).
- Optimize outcomes for patients with relapsed or refractory FL through the application of emerging clinical research data.
- Evaluate the benefits and risks of therapy with different monoclonal antibodies as mono- or combination therapy in the treatment of relapsed or refractory FL or other indolent non-Hodgkin lymphomas or previously untreated chronic lymphocytic leukemia.
- Compare and contrast the benefits and risks of radioimmunotherapy and standard immunochemotherapy in the management of newly diagnosed FL.

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To go directly to slides and commentary for this issue, **click here**.

For this concluding post-ASH summary we focus on a smattering of data sets that shed additional light on a number of relevant clinical questions and therapeutic strategies in the management of indolent NHL, including follicular lymphoma (FL) and CLL:

1. Rituximab (R)/lenalidomide (len) in CLL

Previous preclinical work suggested that the effect of len on natural killer cell expansion enhanced the cytotoxic impact of R, and on that basis several trials evaluating the "R squared" combination were launched, including 3 studies reported at ASH. The first was a Phase II effort evaluating R/len in 59 patients with relapsed/refractory CLL, and the combination produced an impressive overall response rate of 66% with a median time to treatment failure of 24 months. A second Phase II study attempted to assess the combination in patients with previously untreated disease, and more than 75% of patients responded. Finally, an encouraging Phase I-II study evaluating fludarabine/R and escalating doses of len as induction therapy followed by R/len maintenance in 45 previously untreated patients resulted in a 49% CR rate, but dose-limiting toxicity (mainly dermatologic) was observed in more than a third of participants. Len is currently only used by most investigators in very advanced refractory CLL.

2. Alemtuzumab/fludarabine/cyclophosphamide (AFC) in patients with high-risk CLL requiring treatment

At ASH, our understanding of how to integrate alemtuzumab into the treatment algorithm for CLL once again hit a bump in the road with the report from a Phase III trial evaluating low-dose subcutaneous A in combination with FC versus FC alone. Although the addition of the anti-CD52 antibody resulted in slightly better cancer outcomes, substantial toxicity was observed, including flulike symptoms and infection related to immune suppression, and as such this approach remains investigational.

3. Obinutuzumab (GA101)

ASH provided a vivid reminder of the impressive activity of anti-CD20 antibody treatment in B-cell lymphomas with the first results of the landmark ECOG RESORT trial commented on earlier in this series, in which the control arm of 4 weekly doses of R resulted in a 70% response rate, and without further treatment, 86% of patients who responded were progression free at 3 years.

The activity of this bellwether biologic agent is the reason there was great interest in 3 ASH data sets evaluating obinutuzumab (O) — a novel glycoengineered type 2 anti-CD20 MAB with a different functional profile than rituximab (more direct cytotoxicity and cell death but slightly less complement-dependent cytotoxicity). The first, a Phase I-II trial, reported objective responses in patients considered resistant to R, while the second, a randomized Phase II study with 175 patients comparing O to R as single agents in the relapsed setting, showed response rates modestly favoring O. Finally, a Phase I study looked at the agent in combination with CHOP or FC and provided confidence that a large Phase III trial comparing R-CHOP to O-CHOP is feasible.

4. Two data sets on up-front radioimmunotherapy (RIT) in FL

A much anticipated and somewhat disappointing SWOG trial of R-CHOP versus CHOP followed by ^{131}I-tositumomab consolidation demonstrated similar efficacy and tolerability with a few more cases of AML/MDS in the RIT arm (7 versus 3). The study raises natural questions about a more comprehensive strategy of R/chemo followed by RIT consolidation and R maintenance, which is the approach used in a subsequent Phase II SWOG study that has completed accrual but has not yet reported. Another ASH Phase II report focused on RIT alone up front — this time with 2 fractions of ^{90}Y ibritumomab. Thirteen of 76 patients received pretreatment with R in an attempt to clear bone marrow involvement greater than 20%, and 11 of the 13 were able to receive RIT. A median PFS of 36 months was observed, with manageable hematologic toxicity. However, RIT monotherapy up front is rarely utilized in clinical practice pending more definitive trial data.

5. [18F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scans in FL

At ASH we saw the results of a study of interim and end-of-treatment FDG-PET scans in 121 patients with FL receiving R-CHOP. Approximately one quarter had positive end-of-treatment scans, and not surprisingly 2-year PFS and OS were worse in this group. (About half of all patients with positive scans at the end of treatment had disease progression at 2 years.) The challenge of managing these patients remains unanswered and, hopefully, more guidance will come from future clinical research.

6. Bortezomib in FL

A prior report from the 676-patient randomized Phase III LYM3001 study of R alone or with bortezomib in relapsed/refractory disease demonstrated a modest advantage to the combination, and at ASH an impressive translational data set was presented looking at prespecified sera and tissue endpoints that identified a subset of approximately a third of patients in the trial who achieved a greater benefit with the addition of bortezomib. These markers are not "ready for prime time" but are sure to be looked at in studies like ECOG-E2408, evaluating bendamustine/rituximab (BR) followed by R versus bortezomib/BR followed by R versus BR followed by R/len in high-risk FL.

Next we return to our recent breast cancer Patterns of Care survey, this time focusing on management of HER2-positive tumors in the early and advanced disease setting.

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Radioimmunotherapy for FL

Presentations discussed in this issue

Press OW et al. **A Phase III randomized intergroup trial (SWOG S0016) of CHOP chemotherapy plus rituximab vs CHOP chemotherapy plus iodine-131-tositumomab for the treatment of newly diagnosed follicular non-Hodgkin's lymphoma.** *Proc ASH* 2011;**Abstract 98**.

Illidge TM et al. **Fractionated ^{90}Y ibritumomab tiuxetan (Zevalin™) radioimmunotherapy as an initial therapy of follicular lymphoma — First results from a Phase II study in patients requiring treatment according to GELF/BNLI criteria.** *Proc ASH* 2011;**Abstract 102**.

Slides from presentations at ASH 2011 and transcribed comments from recent interviews with Stephanie A Gregory, MD (1/11/12) and Brad S Kahl, MD (1/26/12)

A Phase III Randomized Intergroup Trial (SWOG S0016) of CHOP Chemotherapy plus Rituximab vs CHOP Chemotherapy plus Iodine-131-Tositumomab for the Treatment of Newly Diagnosed Follicular Non-Hodgkin's Lymphoma

Press OW et al.
Proc ASH 2011;Abstract 98.

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Background

- Advanced follicular lymphoma (FL) is incurable with conventional chemotherapy and there is no consensus on the best treatment approach.
- The SWOG-9911 study with CHOP followed by ^{131}I-tositumomab showed promising results with a 60% progression-free survival (PFS) and 79% overall survival (OS) after a 10-year follow-up for patients with newly diagnosed FL.
- **Objective:** Compare the safety and efficacy of CHOP-R versus CHOP-RIT for newly diagnosed FL.

Press OW et al. *Proc ASH* 2011;Abstract 98.

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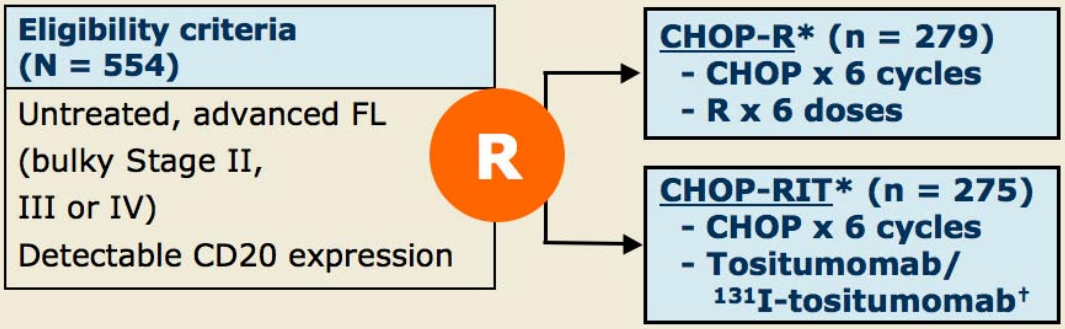
S0016 Phase III Study Design



* Maintenance R not used on this study

† Dosimetric infusion of tositumomab/^{131}I-tositumomab followed 1-2 weeks later by a therapeutic infusion of ^{131}I-tositumomab (total dose: 75 cGy)

Press OW et al. *Proc ASH* 2011;Abstract 98.

Response and Survival Analysis (Abstract)

Response	CHOP-R (n = 263)	CHOP-RIT (n = 260)	*p*-value
ORR	85%	86%	0.9
CR/ CRu	41%	46%	0.25
Two-year survival	**CHOP-R (n = 267)**	**CHOP-RIT (n = 265)**	***p*-value**
PFS	76%	80%	0.11
OS	97%	93%	0.08

- Median follow-up: 4.9 years
- Hazard ratio (HR) for PFS = 0.79, HR for OS = 1.55
- Response assessment not possible: 10% CHOP-R arm, 8% CHOP-RIT arm

Press OW et al. *Proc ASH* 2011;Abstract 98.

Adverse Events (Abstract)

Adverse event	CHOP-R (n = 263)	CHOP-RIT (n = 263)	*p*-value
Hematologic toxicity (Grade 4)	36%	30%	0.19
Nonhematologic toxicity (Grade 4)	1.5%	1.9%	1.0
Treatment-related mortality	0.4%	1.5%	0.37
Second malignancies	8.7%	8.3%	1.0
AML/MDS	1.1%	2.7%	0.34

Press OW et al. *Proc ASH* 2011;Abstract 98.

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Author Conclusions

- No statistically significant differences in PFS, OS or serious toxicities were demonstrable with either regimen administered in this trial.
- PFS and OS are outstanding with both regimens, and median time to progression has not been reached for either treatment.
- Future studies will need to assess if combining CHOP-R with RIT consolidation and maintenance rituximab will confer additive benefit.
- A follow-up trial (SWOG protocol S0801; NCT00770224) that has recently completed accrual will address this question.

Press OW et al. *Proc ASH* 2011;Abstract 98.

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Investigator Commentary: Phase III Randomized Trial of CHOP plus Rituximab vs CHOP plus ^{131}I-Tositumomab for Newly Diagnosed FL

The patients in this study had both high and low tumor burden FL. This has to be kept in mind when comparing results from this study to previous studies. Comparison of R-CHOP to CHOP-RIT showed excellent results with both regimens, with a few more cases of AML/MDS in the CHOP-RIT arm. The outcome in the CHOP-RIT arm may have been better with R-CHOP induction followed by a maintenance regimen. However, this study was started 10 years ago and was designed according to what was known at the time. If they had to choose 1 of these 2 strategies, I believe most people would pick R-CHOP because they are more familiar with it and it is more convenient to administer.

Interview with Brad S Kahl, MD, January 26, 2012

The hope was that the RIT arm would show a much better response. I believe that the CHOP chemotherapy negated the beneficial effect of RIT. This study should have had rituximab added to chemotherapy followed by consolidation RIT followed by rituximab maintenance. The follow-up S0801 study did just that and should be interesting.

Interview with Stephanie A Gregory, MD, January 11, 2012

Fractionated ^{90}Y Ibritumomab Tiuxetan Radioimmunotherapy as an Initial Therapy of Follicular Lymphoma — First Results from a Phase II Study in Patients Requiring Treatment According to GELF/BNLI Criteria

Illidge T et al.

Proc ASH 2011;Abstract 102.

Background

- Radioimmunotherapy (RIT) has demonstrated high response rates and durable remission in relapsed follicular lymphoma (FL).
- There are currently few data with RIT in untreated FL.
- ^{90}Y ibritumomab tiuxetan used as front-line treatment for FL resulted in an ORR of 72% and a CR of 52% 1 year after therapy (*Blood* 2010;116:Abstract 593).
- ^{131}I tositumomab has demonstrated an ORR of 97% and a CR rate of 72% in patients with low-risk disease (*N Engl J Med* 2005;352:441).
- **Objective:** Evaluate the efficacy and safety of 2 fractions of ^{90}Y ibritumomab tiuxetan in patients with untreated FL.

Illidge T et al. *Proc ASH* 2011;Abstract 102.

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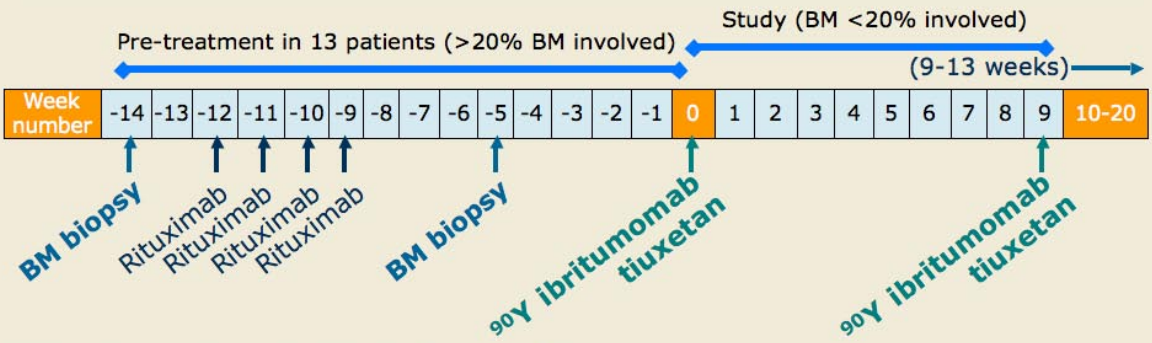
Study Design

Eligibility criteria (N = 76)

Untreated FL Grade I, II or IIIa

At least one symptom requiring treatment initiation:

- Nodal mass >7 cm, at least 3 nodes
- B symptoms
- Elevated serum LDH or ß2 microglobulin
- Symptomatic splenic enlargement
- Compressive syndrome



Illidge T et al. *Proc ASH* 2011;Abstract 102.

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Response to Therapy

End of treatment response* (n = 72)	
ORR	95.8%
Best response†	
ORR CR	97.2% 65%
Single ^{90}Y ibritumomab tiuxetan infusion (n = 17)	
ORR	100%
CR/CRu	75%

* Evaluated at 3 months.

† Five patients converted from PR to CR, 1 SD to PR.

Illidge T et al. *Proc ASH* 2011;Abstract 102.

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Survival

Two-year PFS	67%
Median PFS	36 months
Two-year OS	99%
Further treatment-free survival at 2 years*	74%

* Nineteen of 28 patients whose disease progressed were re-treated.

Illidge T et al. *Proc ASH* 2011;Abstract 102.

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Adverse Events

Grade 3/4 hematologic AE (n = 72)	
Platelets (1st fraction)	20.8%
Platelets (2nd fraction)	56.4%
WBC (1st fraction)	20.8%
WBC (2nd fraction)	29.1%
Neutrophils (1st fraction)	20.8%
Neutrophils (2nd fraction)	36.4%

- Four episodes of infection, 2 hospitalizations with neutropenic sepsis
- Two cases of MDS, 1 potentially treatment related
- Two deaths: 1 due to metastatic breast cancer, 1 due to AML

Illidge T et al. *Proc ASH* 2011;Abstract 102.

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Author Conclusions

- Patients with >20% bone marrow (BM) infiltration can be treated with RIT after 4 weekly cycles of rituximab to clear the BM.
- High ORR (97.2%) and CR (65%) rates were observed in a high-risk population.
- Hematologic toxicity was manageable with very few infectious complications.
- Median PFS of 36 months is comparable with nonanthracycline-based regimens.
- This is a convenient and feasible regimen for patients with FL.

Illidge T et al. *Proc ASH* 2011;Abstract 102.

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Investigator Commentary: Fractionated Radioimmunotherapy as an Initial Therapy of FL

This study used 2 doses of RIT with the hope of getting a better response. But the patient gets more radiation exposure with 2 doses, and I am concerned about increasing radiation. I'm not convinced of the benefit of administering it in fractionated doses versus the standard single dose.

I believe that RIT is underutilized largely for financial reasons. In addition, it is easier to administer rituximab maintenance. Oncologists state that the reason they do not use RIT is the risk of MDS. But if you look at the studies with RIT alone, the incidence is not higher than in patients with low-grade lymphoma who have received multiple treatments. More cases of MDS seem to occur when you administer chemotherapy in addition to RIT. All chemotherapeutic regimens have alkylating agents, which result in a double hit. Two agents I'm particularly concerned about are bendamustine and fludarabine.

Some patients are fearful about radiation therapy and we need to talk to them about radiation safety. Radiolabelled ^{90}Y ibritumomab tiuxetan only has a beta emitter and does not result in as much radiation exposure as tositumomab. It is easier to work with and I prefer it to tositumomab.

Interview with Stephanie A Gregory, MD, January 11, 2012