5 Minute JournalClub

Key ASH Presentations
Issue 9, 2012

Immunochemotherapy with Alemtuzumab and FC in High-Risk CLL

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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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Last review date: April 2012
Expiration date: April 2013

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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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Immunochemotherapy with Alemtuzumab and FC in High-Risk CLL

Presentation discussed in this issue

Geisler CH et al. **Immunochemotherapy with low-dose subcutaneous alemtuzumab (A) plus oral fludarabine and cyclophosphamide (FC) is safe and induces more and deeper complete remissions in untreated patients with high-risk chronic lymphocytic leukemia (CLL) than chemotherapy with FC alone. An early analysis of the randomized Phase-III HOVON68 CLL trial.** *Proc ASH* 2011;**Abstract 290**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with John P Leonard, MD (4/6/12)

Background

- Genomic aberrations and unmutated immunoglobulin heavy chain genes are associated with an unfavorable outcome in CLL (*Leukemia* 2002;16:993).
- Although previous studies showed promising results with fludarabine and cyclophosphamide (FC) in combination with rituximab, the optimal regimen for patients with high-risk CLL is unknown (*Blood* 2008;112:975).
- Alemtuzumab (A), an anti-CD52 antibody, has shown promising results as first-line therapy for CLL and for fludarabine-refractory CLL (*J Clin Oncol* 2007;25:5616; *Blood* 2002;99:3554).
- **Objective:**
  - Improve the outcome of high-risk CLL by adding low-dose A to FC.

Geisler C et al. *Proc ASH* 2011;Abstract 290.

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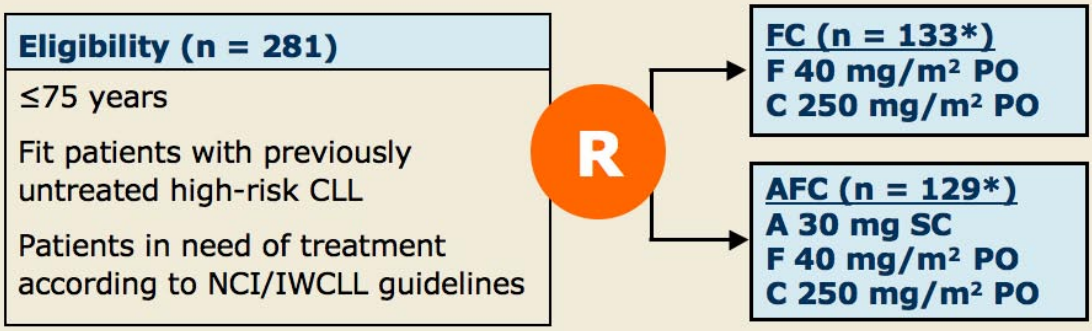
Phase III HOVON68 Trial Design



* The number of patients with evaluable disease at time of analysis

Primary endpoint:

Progression-free survival (PFS) in the intent-to-treat population

Secondary endpoints:

Rate of complete remission (CR), rate of minimal residual disease (MRD)-negative CR, overall survival (OS) and toxicity

Geisler C et al. *Proc ASH* 2011;Abstract 290.

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Response Rates (Abstract)

Rate	AFC (n = 129)	FC (n = 133)	*p*-value
Overall response	88%	80%	—
CR	57%	45%	0.049
MRD-negative CR	29%	17%	<0.02

Median follow-up was 30 months

There was no difference in response between treatments when patients were classified according to Binet stage or beta-2-microglobulin level.

Geisler C et al. *Proc ASH* 2011;Abstract 290.

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Survival Rates (Abstract)

Response	AFC (n = 129)	FC (n = 133)	*p*-value
Median PFS	37 months	31 months	0.08

- Though statistically insignificant, there was a trend toward improved PFS with AFC treatment in the patient subgroups with 17p deletions, 11q deletions, trisomy 12 or unmutated IGH genes.
- There was no difference in PFS between treatments when patients were classified according to Binet stage or beta-2-microglobulin level.
- The median OS has not yet been reached.

Geisler C et al. *Proc ASH* 2011;Abstract 290.

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Adverse Events (AEs) (Abstract)

Event	AFC	FC	*p*-value
Severe AEs (mostly Grade 3)	145	90	<0.0001
Flulike symptoms	27	2	—
Opportunistic infections	25	11	—
Organ toxicity	34	14	—
Treatment-related death	6	6	—

- There were no differences between treatment arms in the number of neutropenic events and the occurrence of other infections.
- Vigilance and prophylaxis against infection were maintained throughout the study.

Geisler C et al. *Proc ASH* 2011;Abstract 290.

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Author Conclusions

- The addition of low-dose alemtuzumab, administered subcutaneously, to FC induced a higher rate and quality of CR versus FC therapy alone.
- However, neither PFS nor OS results differed significantly between treatment arms in this early analysis.
- Because combination therapy with AFC is more immunosuppressive than FC only, there was a greater number of opportunistic infections with AFC.
  - With proper vigilance and prophylactic measures, these infections were manageable and did not lead to excessive mortality.

Geisler C et al. *Proc ASH* 2011;Abstract 290.

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Investigator Commentary: Immunochemotherapy with Alemtuzumab in Combination with Fludarabine and Cyclophosphamide Is Safe and Induces More and Deeper Complete Remissions in Untreated High-Risk CLL than FC Alone

This study is important because it was a randomized trial comparing FC to alemtuzumab and FC (AFC). The efficacy of the AFC and FC arms was comparable, with similar overall and complete remission rates. However, the complete remission rates statistically favored the AFC arm. More toxicity was seen in the AFC arm, particularly flulike symptoms and infections, which are known to occur with alemtuzumab.

The big question that arises is how a standard regimen like rituximab in combination with FC (FCR) would compare to AFC and FC with regard to efficacy and tolerability. Data from certain groups, such as the MD Anderson group, showed that when you add alemtuzumab to an FCR regimen, this 4-drug regimen results in more infectious complications.

Overall, although this is an interesting approach to treatment, I don't believe it is practice changing.

Interview with John P Leonard, MD, April 6, 2012

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