



Hematologic Oncology
Issue 4, 2013

**Disease Characteristics, Patterns
of Care and Treatment Outcomes
of Elderly Patients with FL from the
National LymphoCare Study**

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) annual meetings and the International Conference on Malignant Lymphoma (ICML), to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they are aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on treatment approaches and novel agents in non-Hodgkin lymphoma (NHL) from the latest ASCO, EHA and ICML meetings, including expert perspectives on how these new evidence-based concepts may 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

- Appraise recent clinical research findings on the efficacy and safety of radioimmunotherapy with ⁹⁰Y-ibritumomab tiuxetan for elderly patients with CD20-positive B-cell NHL.
- Compare and contrast the differences in patterns of care and treatment outcomes in older versus younger patients with follicular lymphoma based on data from the US National LymphoCare Study database.
- Evaluate the benefits and risks of novel therapeutic approaches with lenalidomide as a single agent in relapsed or refractory mantle-cell lymphoma (MCL) after bortezomib treatment or in combination with rituximab (R² regimen) for patients with previously untreated follicular lymphoma.
- Assess the effectiveness and tolerability of up-front combination therapy with bendamustine and rituximab versus standard rituximab-based chemotherapy in advanced indolent NHL compared to in MCL.
- Consider the clinical impact of rituximab maintenance versus observation after induction chemotherapy on the risk of relapse for patients with aggressive B-cell lymphoma.
- Recall the utility of post-therapy surveillance imaging approaches for earlier detection of relapses in patients with diffuse large B-cell lymphoma.

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Hardware/Software Requirements:

A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: November 2013

Expiration date: November 2014

To go directly to slides and commentary for this issue, [click here](#).

This fourth and final issue of *5-Minute Journal Club* walks through a number of interesting lymphoma presentations from ASCO, EHA and ICML at Lugano, but as we were putting the final touches on the program last Friday, a white-hot email came through announcing the FDA approval of yet another novel anticancer agent, in this case the glycoengineered type II anti-CD20 monoclonal antibody (MoAb) obinutuzumab (O) combined with chlorambucil (Clb) in previously untreated CLL. To add to the critical nature of this moment, just yesterday ASH posted abstracts from the annual meeting coming up next month, and among these are definitive findings from a Phase III up-front trial in CLL of 663 older patients (median age 73) first reported preliminarily at ASCO evaluating Clb alone or with O or with rituximab (R).

The world will see these landmark data and begin the debate at ASH, but the bottom line is that OClb resulted in a statistically significant and clinically meaningful prolongation of progression-free survival (PFS) and higher rates of complete response (CR) and minimal residual disease negativity compared to RClb. However, in terms of tolerability, infusion-related reactions and neutropenia without an increase in infections were more common with OClb.

We immediately sought help in figuring out what this means to physicians in practice, and for the bonus finale of this series check out the thoughts of Dr Michael Williams about obinutuzumab, trogocytosis and where we are in CLL at the moment. Meanwhile, here are our picks for the best summer lymphoma papers:

1. R squared (again)

At ASH in December Dr Nathan Fowler presented more mature data from his pathfinding Phase II trial evaluating lenalidomide (Len)/rituximab (R squared) up front in indolent lymphomas, including follicular lymphoma (FL), and at Lugano we saw [a CALGB study](#) with similar stellar results (72% CRs). An ongoing Phase III trial compares this nonchemotherapy regimen to R-chemotherapy, but where this will fit in with O and the new small-molecule B-cell receptor inhibitors such as ibrutinib and idelalisib is unclear.

[In another interesting Lugano paper](#), the US-based prospective “LymphoCare” registry reported the largest ever series of patients with FL older than age 80 (n = 209) and not surprisingly demonstrated less use of R-chemotherapy and more R monotherapy, but of interest, response rates were only slightly lower than those in younger patients.

2. Radioimmunotherapy (RIT) consolidation after R-chemotherapy as an alternative to R maintenance

During our recent (and soon to be published) lymphoma/CLL think tank, Dr Julie Vose commented that she sometimes uses RIT rather than R maintenance after R-chemotherapy in older patients with indolent lymphomas, particularly when transportation to and from clinic for R infusions is problematic. In this regard, **[a Phase II Polish study](#)** presented in Lugano looked at RIT consolidation in 46 patients with mantle-cell lymphoma (MCL) ineligible for autologous stem cell transplantation or after chemosensitive relapse and reported an encouraging median PFS of 3.5 years. **[Another paper from EHA](#)** documented excellent outcomes in 39 patients with a variety of lymphomas, using RIT either as consolidation or monotherapy for relapsed/refractory disease with 74% CRs.

3. Bendamustine + R (BR) in indolent lymphoma

At ASCO and Lugano we saw more data from **[the Phase III BRIGHT study](#)** demonstrating at least equivalent efficacy between BR and R-CHOP/R-CVP in patients with NHL and perhaps an advantage in MCL with BR, which is now commonly used first line in indolent lymphomas primarily due to its tolerability profile, including the lack of alopecia.

4. Len in MCL

The 134-patient **[EMERGE study](#)** that led to the recent FDA indication of Len in MCL was updated at EHA and recently published in the *JCO* demonstrating a 28% overall response rate in patients with heavily pretreated disease (median of 4 prior therapies). The hope is that greater efficacy will be seen if this agent is administered earlier, although the current indication restricts its use to patients who have received 2 prior treatments, including bortezomib.

5. Post-therapy surveillance scans in diffuse large B-cell lymphoma (DLBCL); R maintenance in DLBCL

[An ASCO oral presentation](#) was one of a number of recent retrospective lymphoma series documenting the rare likelihood of surveillance scans detecting recurrence in an asymptomatic patient with normal laboratory data, but many oncologists continue to employ this practice, likely due to the potential curability of relapsed disease.

This summer we also saw more generally unimpressive results with **R maintenance in DLBCL**, and not surprisingly, investigators do not endorse this strategy. Perhaps better outcomes will be seen with the new generation of anti-CD20 MoAbs like O.

Speaking of O, as promised here are a few initial thoughts and comments from Dr Williams on questions that will be discussed a great deal starting at 4:15 PM on Sunday, December 8 in New Orleans:

Aren't all anti-CD20 MoAbs the same?

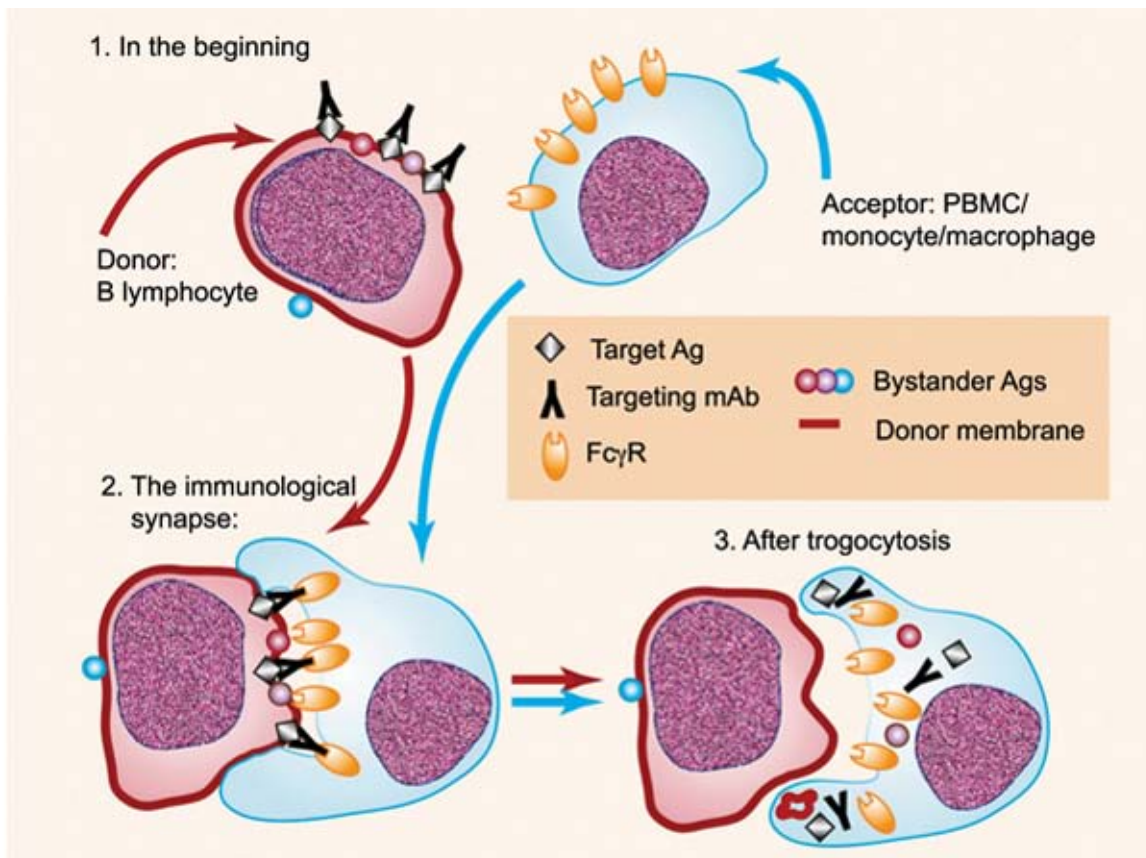
Until maybe yesterday most lymphoma investigators have been generally unexcited about the possibility that a whole lot more could be squeezed out of new anti-CD20 agents compared to R in B-cell neoplasia, but the new O data are likely to result in a lot more interest in exactly how MoAbs improve cancer outcomes (trastuzumab, for example, in breast cancer). Dr Williams notes that the enhanced efficacy of O compared to R may relate to its much greater binding affinity to CD20 and increased stimulation of antibody-dependent cell-mediated cytotoxicity — factors that may be more important in CLL than lymphomas because of the lower CD20 density on CLL cells.

When should O be considered right now in practice?

Dr Williams, like many lymphoma investigators, not uncommonly uses the venerable Clb alone or with R mainly in older, frail patients with lower-risk disease, and based on the new FDA indication he is ready to selectively combine O with Clb as soon as it's available on his formulary. He also often uses the type I MoAb ofatumumab as monotherapy in patients with CLL who have received prior R but will now be inclined to try O instead. However, until more data are available, Dr Williams will not combine O with other chemotherapies either in CLL or lymphomas, but he is interested in seeing data emerge from Phase II combination studies, particularly those testing O with bendamustine.

What is the basis for the apparent improved outcomes with O compared to R?

The dosing with O is greater than with R, and some have suggested this was a factor in the trial results. Dr Williams, however, is convinced that the fundamental differences in mechanisms of action of O and R explain the advantage observed, at least in CLL, and he is particularly interested to see data with O related to a phenomenon called "shaving" that he and collaborators reported on, in which the CD20/R complex on the cell surface is removed by the spleen and reticuloendothelial system, allowing leukemic cells to survive. This process is also known as trogocytosis (from the ancient Greek "to nibble"), and Dr Williams is curious to study whether a variation in how the O/CD20 complex is "nibbled" might explain the improved outcomes.



Trogocytosis of IgG bound to targeted antigens is mediated by Fcγ receptors on acceptor cells. Interaction of IgG bound to target antigens on the donor cell (1) with Fcγ receptors on the acceptor cell leads to formation of an immunologic synapse (2). The acceptor cell then ingests the immune complex and portions of the donor cell membrane, along with the participating Fcγ receptors (3). Other surface antigens in close proximity to the target immune complex are also taken up by the acceptor cell. Ag, antigen; PBMC, peripheral blood mononuclear cell. Professional illustration by Paulette Dennis.

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That does it for this short review series. Stay tuned for our upcoming audio and video highlights of the aforementioned lymphoma/CLL think tank as Dr Vose, Dr Williams and their colleagues tackle many other key questions of the day.

Neil Love, MD

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Disease Characteristics, Patterns of Care and Treatment Outcomes of Elderly Patients with FL from the National LymphoCare Study

Presentation discussed in this issue

Nabhan C et al. **Disease characteristics, patterns of care, and outcomes of follicular lymphoma (FL) in the oldest old: Report from the US National Lymphocare Study (NLCS).** *Proc ICML 2013*; **Abstract 102.**

Slides from a presentation at ICML 2013 and transcribed comments from recent interviews with Christopher Flowers, MD, MS (7/19/13) and Jonathan W Friedberg, MD, MMSc (7/19/13)

Disease Characteristics, Patterns of Care, and Outcomes of Follicular Lymphoma (FL) in the Oldest Old: Report from the US National Lymphocare Study (NLCS)

Nabhan C et al.

Proc ICML 2013; Abstract 102.

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Background

- Data on disease characteristics, treatment patterns and outcomes of patients older than age 80 are rarely reported.
- The US National Lymphocare Study (NLCS) is a prospective multicenter registry of patients with follicular lymphoma (FL) without study-specific treatment.
- **Study objective:** To analyze the disease characteristics, patterns of care and treatment outcomes for patients with FL who are older than age 80 using the NLCS database.

Nabhan C et al. *Proc ICML 2013*;Abstract 102.

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Study Methods

- All evaluable patients with newly diagnosed FL in the NLCS database were included (n = 2,649).
- Associations of age groups with disease characteristics and response rate (RR) were examined using the Pearson's Chi-squared test.
- The median progression-free survival (PFS) and overall survival (OS) by treatment regimen were estimated for each age group.
- Cox regression adjusted for baseline disease factors and use of maintenance rituximab (MR) were used:
 - To assess treatment differences in PFS and OS.
 - To determine the significance of age by treatment interactions.

Nabhan C et al. *Proc ICML 2013*;Abstract 102.

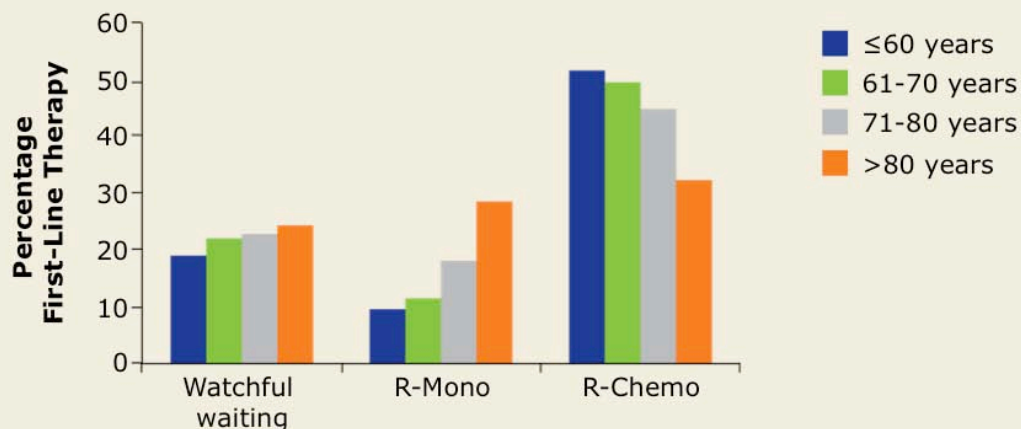
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Baseline Characteristics

Characteristic	≤60 years (n = 1,255)	61-70 years (n = 666)	71-80 years (n = 519)	>80 years (n = 209)
White race	88%	92%	92%	94%
Stage III or IV disease	71%	64%	63%	63%
Grade 3 histology	18%	22%	22%	27%
≥5 nodal sites	39%	32%	31%	18%
Hemoglobin <12 g/dL	16%	22%	26%	38%
ECOG PS 0	76%	65%	60%	45%
Bone marrow involvement	41%	33%	37%	33%

Nabhan C et al. *Proc ICML 2013*;Abstract 102.

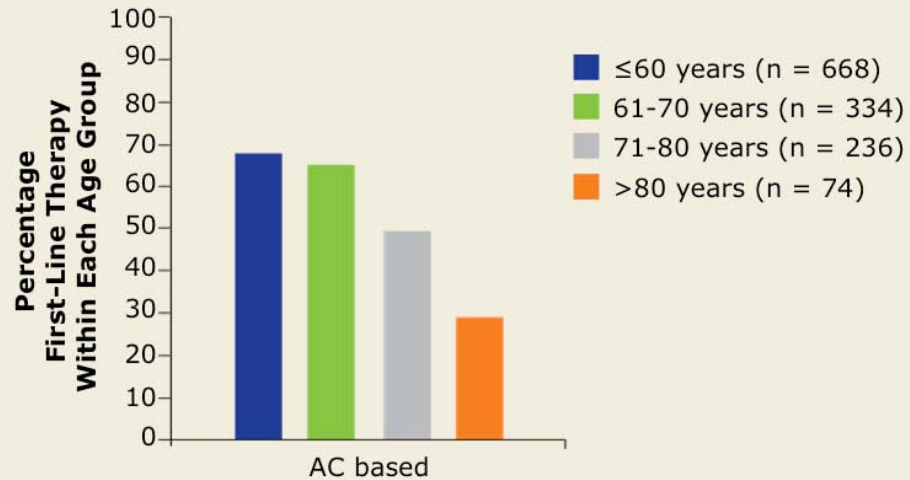
Initial Treatment Regimen by Age



- Patients aged >80 years (treatment patterns significantly different than for patients aged ≤60; $p < 0.0001$):
 - Underwent watchful waiting more often (24% vs 19%)
 - Received rituximab monotherapy more often (29% vs 10%)
 - Received R-Chemo as initial strategy less often (32% vs 52%)

With permission from Nabhan C et al. *Proc ICML 2013*;Abstract 102.

Anthracycline (Ac) Use by Age



- Patients aged >80 who received chemotherapy alone or in combination with rituximab were less likely to receive Ac than were patients aged ≤60 (28% vs 68%, $p < 0.0001$).
- Only Grade 3 histology significantly predicted Ac use for all age groups.

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Response Rates by Treatment and Age Groups

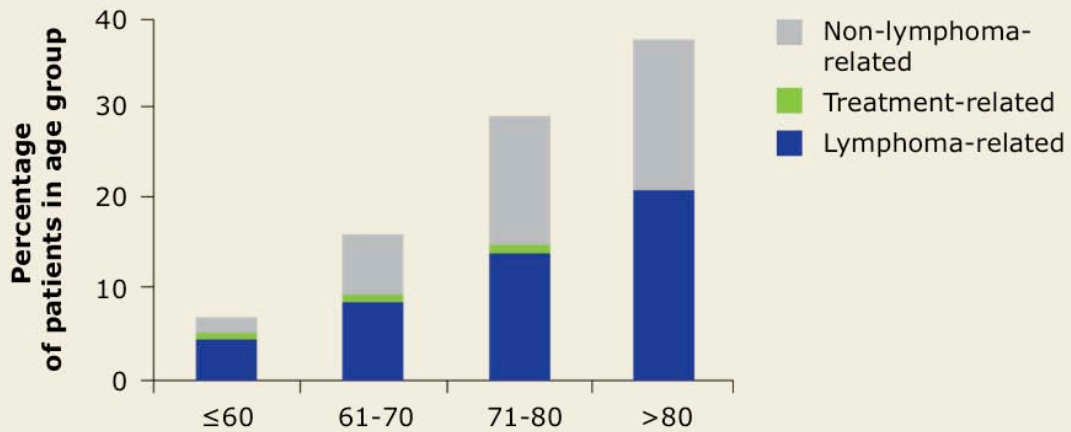
% CR or PR	≤60	61-70	71-80	>80	p-value
All patients	75.7	73.6	71.0	66.0	0.020
Watchful waiting	14.1	22.0	21.1	14.6	0.225
R monotherapy	80.4	80.3	77.3	80.4	0.946
R/chemotherapy	92.1	92.6	88.5	83.9	0.056
AC-based	93.3	95.2	90.8	77.8	0.031
Non-AC-based	86.2	83.0	84.3	77.6	0.504

Note: Bold and orange font indicates significant ($p < 0.05$) differences by age group.

Nabhan C et al. *Proc ICML 2013*;Abstract 102.

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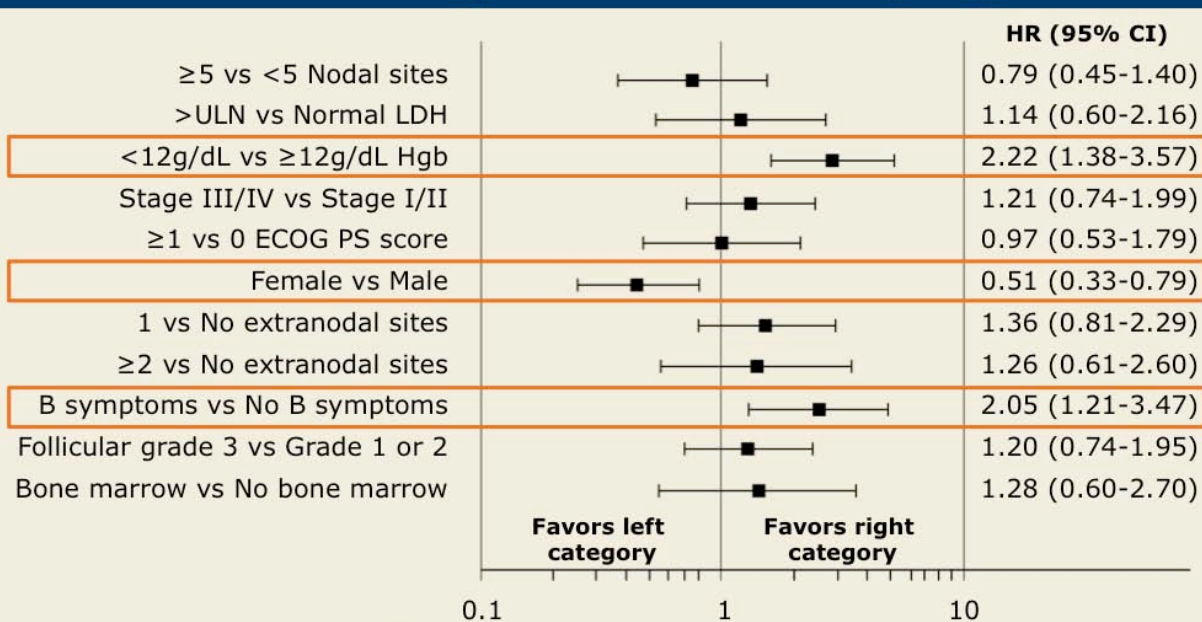
Cause of Death by Age



	≤60	61-70	71-80	>80
Number of deaths	110	130	199	107
Proportion lymphoma-related	48%	42%	36%	40%

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Variables Affecting Overall Survival in Patients >80 Years: Male Sex, Lower Hemoglobin and B Symptoms



Model adjusted for first-line treatment and maintenance rituximab

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Author Conclusions

- PFS was influenced less by choice of therapy for patients older than age 80 with FL than for younger patients.
- Patients older than age 80 are more likely to receive rituximab monotherapy or to be observed.
- B symptoms, male sex and Hgb <12 g/dL predict inferior OS in patients with FL who are older than age 80.
- In patients with FL who are older than age 80, 40% of deaths were attributed to lymphoma, which did not differ considerably from patients younger than age 60.
- Prospective trials designed specifically for this patient population are needed.

Nabhan C et al. *Proc ICML 2013*;Abstract 102.

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Investigator Commentary: Report from the US NLCS in Patients Older Than Age 80 with FL

This was an interesting study to characterize US patterns of care for patients older than age 80 in the NLCS. Although this was a prospective observational study, it represents the largest population of oldest "old" patients ever observed in terms of the kinds of therapies administered. It showed that this patient group was less likely to receive R/chemotherapy. Importantly, these patients were diagnosed with FL in the era when R was gaining in use in FL after its approval but was not necessarily routinely used up front for all patients. As such, these older patients received up-front R/chemotherapy less commonly. Twenty-eight percent of patients older than age 80 received an anthracycline as part of up-front therapy compared to 68% in the group of patients aged 60 or younger, and that was markedly different. It's clear that some of our prejudgments about the kinds of therapies administered to older patients might affect quality of care and survival.

Interview with Christopher Flowers, MD, MS, July 19, 2013

We all approach a patient with FL at age 80 differently than we would a 30-year-old. We are planning to determine whether these patients die of FL. If we demonstrate that most of the deaths in this group are from other comorbid problems, then the conservative approach taken by many practitioners is the right one. However, if it is shown that FL is the key problem, doctors need to do a better job of controlling the disease.

Interview with Jonathan W Friedberg, MD, MMSc, July 19, 2013