5 Minute JournalClub

SPECIAL EDITION
Issue 2, 2011

Reports from Phase III Trials of CHOP-Containing Regimens for the Treatment of Diffuse Large B-Cell Lymphoma (DLBCL)

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Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for diverse forms of cancer.

LEARNING OBJECTIVES

- Integrate emerging research information on the use of R-CHOP 14 versus R-CHOP 21 to formulate personal treatment algorithms for patients with newly diagnosed DLBCL.
- Formulate an evidence-based algorithm for the use of R-CHOP alone or followed by transplant for patients with high-intermediate or high IPI grade diffuse aggressive non-Hodgkin lymphoma.

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

An oncology specialist would be hard pressed to find a better hour of television than the first half of the oral leukemia/myelodysplasia plenary session from ASCO 2011. This riveting segment of the conference, available for your viewing pleasure as part of the virtual meeting, began with 2 complementary presentations of Phase III trials evaluating the JAK1/2 inhibitor ruxolitinib **(ab 6500**, **ab LBA6501)** in patients with myelofibrosis. These were followed by a fascinating BCR-ABL mutation analysis from the ENESTnd CML study **(ab 6502)** comparing nilotinib to imatinib and then a brilliant follow-up discussion by Dr Ross Levine outlining a new paradigm in myeloproliferative disorders focused on the search for mutations and related novel blocking agents. These 3 presentations and 14 other compelling ASCO heme-onc data sets are detailed in our slide sets and profiled below in this, the second half of our super-succinct special edition *5-Minute Journal Club*.

1. Ruxolitinib in myelofibrosis

As mentioned above, this trial duet occupies a unique spot on the ASCO highlights reel, and while our understanding of the exact mechanism of action of this oral TKI may be somewhat hazy and may relate to reduction in elevated cytokine levels, what is crystal clear is that this uncommon but merciless disease has instantly entered a new era. The US-based COMFORT-I study evaluating ruxolitinib versus placebo had a number of interesting and innovative features, including the use of MRI to objectively evaluate spleen size and electronic daily diaries to record patient symptoms. The dramatic waterfall plots visibly illustrate how treatment at least temporarily reversed an otherwise downhill course in most patients.

2. CML

Dr Giuseppe Saglio presented the other previously discussed ASCO standout — the landmark substudy from the ENESTnd trial **(ab 6502)** demonstrating that prior to treatment patients had almost no BCR-ABL mutations but after therapy a fascinating panoply of alterations was observed in some individuals. Dr Levine predicted that in the near future, mutation assays will be regularly integrated into the treatment algorithm.

Additionally, 24-month follow-up from 2 key Phase III studies (ENESTnd **[ab 6511]** and DASISION **[ab 6510]**) was also unveiled in Chicago, suggesting greater efficacy and perhaps less toxicity with up-front treatment with the second-generation TKIs nilotinib and dasatinib when compared to imatinib.

3. Inotuzumab ozogamicin (our vote for name of the year)
This antibody-drug conjugate in the lineage of brentuximab vedotin in lymphoma and T-DM1 in HER2-positive breast cancer links an anti-CD22 antibody to a cytotoxic agent from the calicheamicins class (runner up). The ASCO findings **(ab 6507)** in relapsed/refractory ALL demonstrated some type of CR in 61% of patients.

4. Myeloma
For more than a year we have witnessed the evolution of data from 2 major trials (CALGB, French IFM group) demonstrating an impressive delay in disease progression but the suggestion of an increased risk of second primary cancers (SPC) with 2 years of lenalidomide maintenance following stem cell transplant (SCT). At ASCO, 3 additional reports **(ab 8007, ab 8008, ab 8009)** have for the moment reinforced the concept that if there is an SPC signal it is relatively modest in magnitude and far outweighed by the antimyeloma benefit of maintenance len.

The other much-discussed myeloma paper was a landmark Italian study **(ab 8020)** that for the first time evaluated the role of autologous SCT in the era of novel antimyeloma agents. A progression-free survival benefit was reported with SCT, but other maturing studies are evaluating this important question.

5. CLL
Maybe the most exciting development in B-cell neoplasm research is the rapid evolution of small molecules that block B-cell receptor signaling, and at ASCO we saw more to be optimistic about with a report on the Bruton's tyrosine kinase inhibitor PCI-32765 in CLL. In this Phase Ib/II single-agent study **(ab 6508)**, response rates in excess of 50% were observed with minimal toxicity.

6. Diffuse large B-cell lymphoma
The lack of progress in this common cancer since the introduction of rituximab was highlighted again this year with 1 trial failing to show an advantage with dose-dense R-CHOP **(ab 8000)** and another showing no important survival benefit to consolidation autotransplant after R-CHOP induction **(ab 8001)**.

7. AML
AML in the elderly — a true clinical conundrum — was the subject of 3 underwhelming ASCO reports. The first **(ab 6503)** showed a modest benefit that was counterbalanced by a relatively high early mortality rate when clofarabine was combined with Ara-C. The

second **(ab 6504)** demonstrated a modest benefit for decitabine, but discussant Dr Gail Roboz verbalized hope that better outcomes might be observed in her ongoing trial evaluating 10 days of decitabine combined with the proteasome inhibitor bortezomib. The third study **(ab 6505)** was a Phase I effort evaluating a sequential regimen of azacitidine and lenalidomide that resulted in CRs in 7 of 16 patients.

Finally, we saw another interesting AML study perhaps suggesting a new model for the real-time personalized treatment of the disease. In this Phase I/II trial **(ab 6506)**, the MEK1/2 inhibitor GSK1120212 was shown to have specific activity in patients with RAS mutations.

Coming soon, an online quintet of virtual presentations delving into new developments in non-small cell lung cancer.

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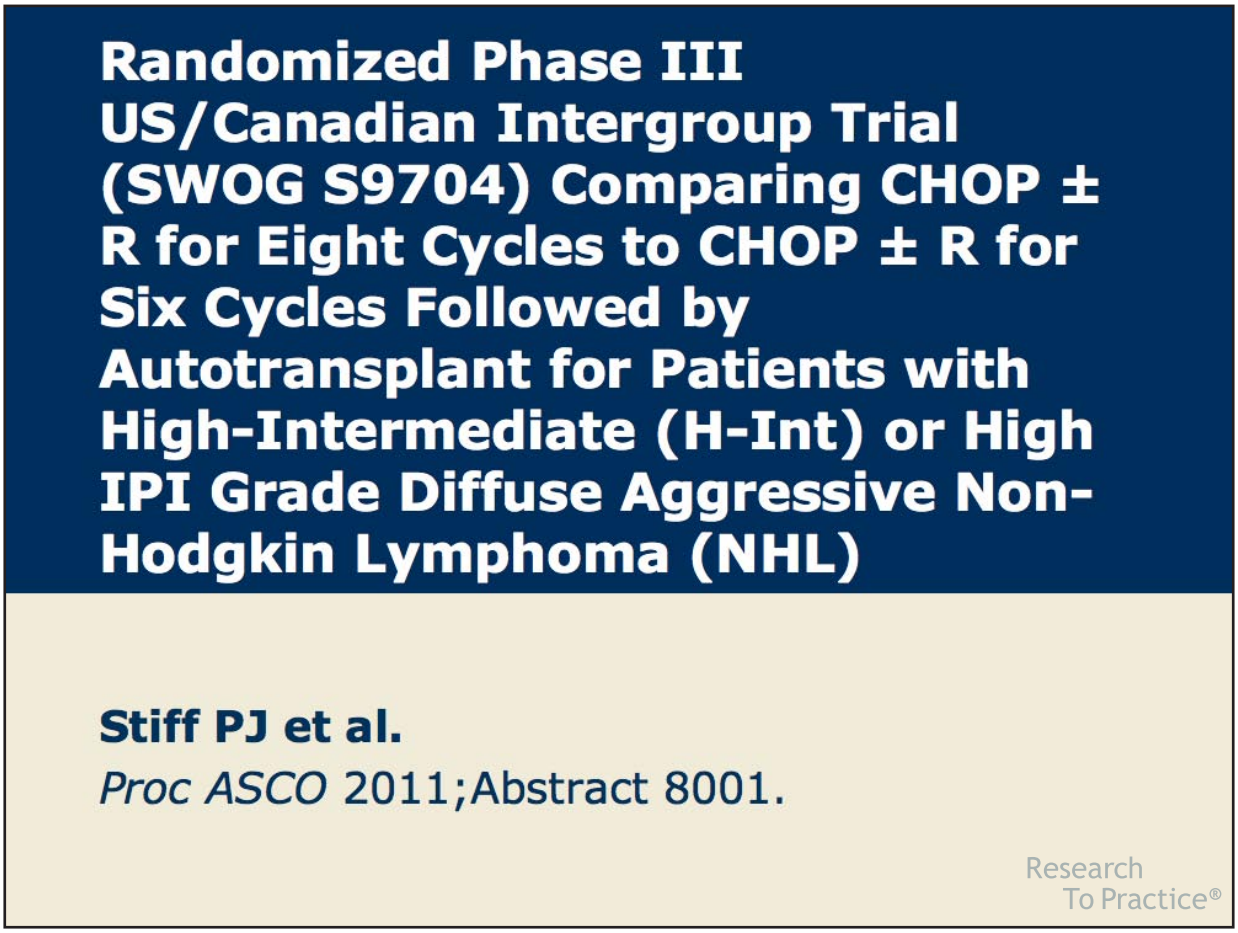
Reports from Phase III Trials of CHOP-Containing Regimens for the Treatment of Diffuse Large B-Cell Lymphoma (DLBCL)

Presentation discussed in this issue

Stiff PJ et al. **Randomized Phase III US/Canadian Intergroup trial (SWOG S9704) comparing CHOP±R for eight cycles to CHOP±R for six cycles followed by autotransplant for patients with high-intermediate (H-Int) or high IPI grade diffuse aggressive non-Hodgkin lymphoma (NHL).** *Proc ASCO* 2011;**Abstract 8001**.

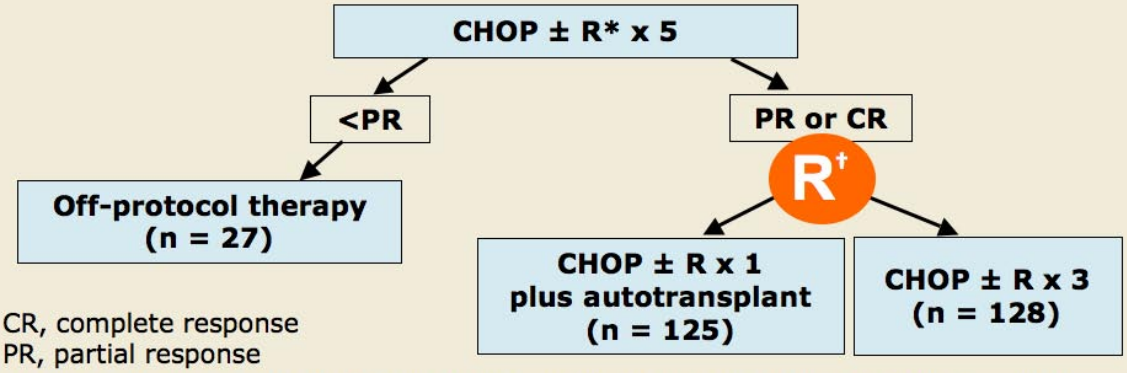
Slides from a presentation at ASCO 2011 and comments from John P Leonard, MD



SWOG-S9704: Phase III Trial Design

Eligibility

Intermediate or high-grade NHL
Bulky Stage II, Stage III or Stage IV disease
High-Int/High-risk IPI
No mantle-cell or lymphoblastic lymphoma



CR, complete response
PR, partial response

* Patients enrolled between 9/97-12/07 were induced with five cycles of CHOP (n = 215) or CHOP-R (after 3/03; n = 182); † Dropped out/not eligible for randomization, n = 117

Stiff PJ et al. *Proc ASCO* 2011;Abstract 8001.

Overall Outcome and Exploratory Analyses

Overall Outcome	CHOP(R) x 1 + ASCT	CHOP(R) x 3	Hazard ratio	*p*-value
Estimated 2-year PFS	69%	56%	1.72	0.005
Estimated 2-year OS	74%	71%	1.24	0.16

Exploratory Analyses	CHOP(R) x 1 + ASCT	CHOP(R) x 3	Interaction *p*-value
Patients with High-Intermediate IPI scores			
Estimated 2-year PFS	66%	63%	—
Estimated 2-year OS	70%	75%	—
Patients with High IPI scores			
Estimated 2-year PFS	75%	41%	0.02
Estimated 2-year OS	82%	64%	0.01

Stiff PJ et al. *Proc ASCO* 2011;Abstract 8001.

Grade 3 or 4 Adverse Events for Randomly Assigned Patients

	CHOP(R) x 1 + ASCT (n = 125)	CHOP(R) x 3 (n = 128)
Infection	50%	13%
Gastrointestinal	26%	5%
Metabolic	13%	1%
Lung	11%	2%
Cardiovascular	10%	4%
Neurologic	7%	2%
Dyspnea	7%	2%
Hyperglycemia	6%	0
Hypoxia	4%	0
Hepatic	3%	0

Stiff PJ et al. *Proc ASCO* 2011;Abstract 8001.

Author Conclusions

- Patients with high-risk diffuse aggressive NHL have a superior 2-year PFS of 69% if they receive an ASCT in first PR/CR after CHOP(R) as compared to PFS of 56% reported with standard conventional therapy alone with CHOP(R).
- This improvement has not yet led to a survival advantage, as 18% of patients who experienced relapse on the standard arm had a long-term PFS after salvage ASCT (data not shown).
- These results did not differ for patients with B-cell versus T-cell NHL or patients with B-cell disease induced with R-CHOP versus CHOP alone (data not shown).
- Exploratory analyses indicated that the majority of the ASCT benefit occurred in patients with high IPI scores for whom transplant had both a PFS and OS advantage.

Stiff PJ et al. *Proc ASCO* 2011;Abstract 8001.

Investigator Commentary: SWOG-S9704 — CHOP±R x 8 versus CHOP±R x 6 Followed by High-Dose Therapy and ASCT for Diffuse Aggressive Non-Hodgkin Lymphoma in High-Intermediate or High IPI Risk Groups

This long-awaited North American Intergroup study compared CHOP or R-CHOP for 8 cycles versus R-CHOP or CHOP for 6 cycles, followed by ASCT in first remission in 370 patients primarily with higher-risk diffuse large B-cell lymphoma (DLBCL). The net of this large study was that no benefit to ASCT exists in first remission. A PFS benefit was observed, which is not surprising, but no overall survival benefit was present. So if you were to perform autotransplants in first remission, you'd be performing transplants unnecessarily. You're not going to affect patients' overall survival.

An interesting feature of the study was a retrospective subgroup analyses. Patients in the high-risk IPI group did appear to gain some benefit with respect to overall survival, suggesting a benefit to performing an ASCT in this setting. However, I believe performing retrospective analyses on subgroups is not quite as robust. But that wasn't the intention of the study and, if you look at the primary endpoints, it comes up as a negative outcome in that ASCT in first remission should not be the general approach for patients with high-intermediate or high-risk NHL.

John P Leonard, MD