5 Minute JournalClub

Key ASCO Presentations
Issue 3, 2010

Maintenance Rituximab for Patients with Follicular Lymphoma (FL) Responding to Front-Line Induction with Rituximab/Chemotherapy

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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 serial 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 patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Summarize the efficacy and safety of maintenance rituximab for patients with FL responding to front-line induction rituximab/chemotherapy.

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Key ASCO Presentations
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To go directly to the slides, **click here**.

Oncologists who were reared on the "shock and awe — MTD" approach to systemic anticancer therapy now understand that the chronic disease model is where the field has been headed for years, and about a decade ago, when imatinib was first being administered indefinitely in CML, Paul Goss proved that in breast cancer, fewer relapses occurred when endocrine therapy was extended beyond five years. This important development led Paul and others to compare breast cancer to follicular lymphoma (FL), with its relapsing and remitting nature and long-term requirement for treatment.

In the past six months, the breast cancer/FL analogy has become even more evident, beginning at ASH with the emergence of bendamustine/rituximab (BR), or as I see it, the "TC" of indolent lymphoma, and then at ASCO, where for the first time, we saw conclusive evidence that the duration of rituximab for FL, as in endocrine therapy for breast cancer, really matters.

A slew of imperfect answers for the question of R maintenance in FL have been reported in the past few years, but investigators were skeptical that more R after R-chemo made a difference. Oncologists in practice weren't as doubtful, and our Patterns of Care data have demonstrated that many have used this strategy for some time. The issue was somewhat laid to rest at ASCO with the **PRIMA presentation**, and Dr Richard Fisher, the paper's discussant, didn't mince words when he stated that R maintenance should now be used in patients with FL requiring treatment. However, after speaking with a number of investigators in the field, I don't see a consensus yet on the clinical and research implications of this data set, in spite of the reduction in two-year risk of disease progression from 34 percent without R maintenance to 18 percent with it. Meanwhile, the Germans, who already created BR and were kicking butt in the World Cup until they encountered Spain, continue to be ahead of the game and 14 months ago launched a randomized trial evaluating BR followed by either two or four years of R maintenance.

Also in this issue:

1. **Pretransplant R purging and post-transplant maintenance** extends progression-free survival in patients with FL.

2. **A Phase II study of the IMiD®** lenalidomide combined with rituximab for indolent lymphoma results in complete tumor responses in more than two thirds of patients.

3. In another **Phase II study for patients older than age 65 with CLL**, treatment with lenalidomide results in responses in 62 percent of patients, without Grade III/IV tumor lysis syndrome or flare.

Next up on 5-Minute Journal Club: The chronic disease model comes to multiple myeloma as two major randomized trials demonstrate benefit for lenalidomide maintenance after transplant.

Neil Love, MD
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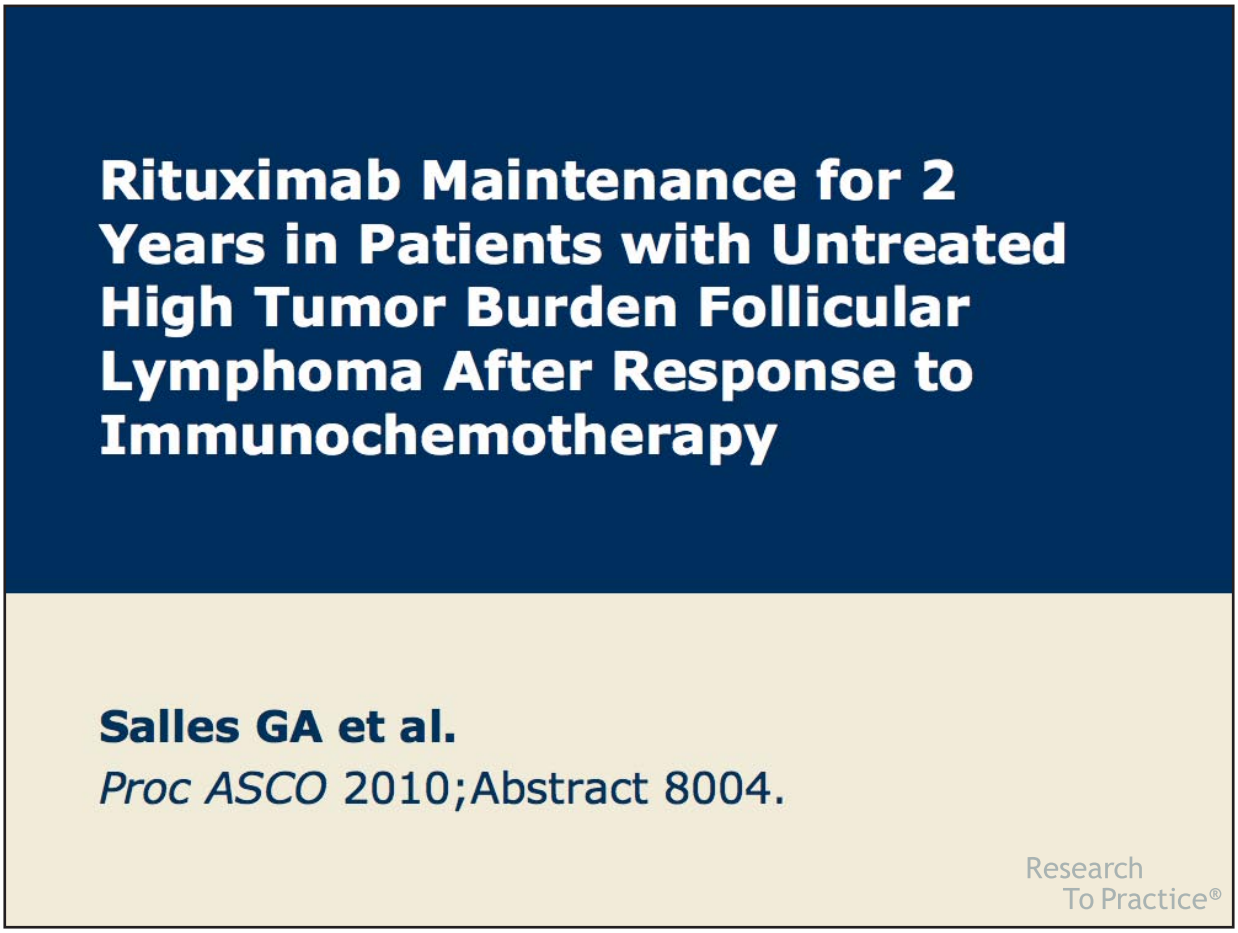
Maintenance Rituximab for Patients with Follicular Lymphoma (FL) Responding to Front-Line Induction with Rituximab/Chemotherapy

Presentation discussed in this issue

Salles GA et al. **Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy.** *Proc ASCO* 2010;**Abstract 8004**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Stephanie A Gregory, MD (6/18/10), John P Leonard, MD (6/28/10) and Mathias J Rummel, MD, PhD (6/7/2010)

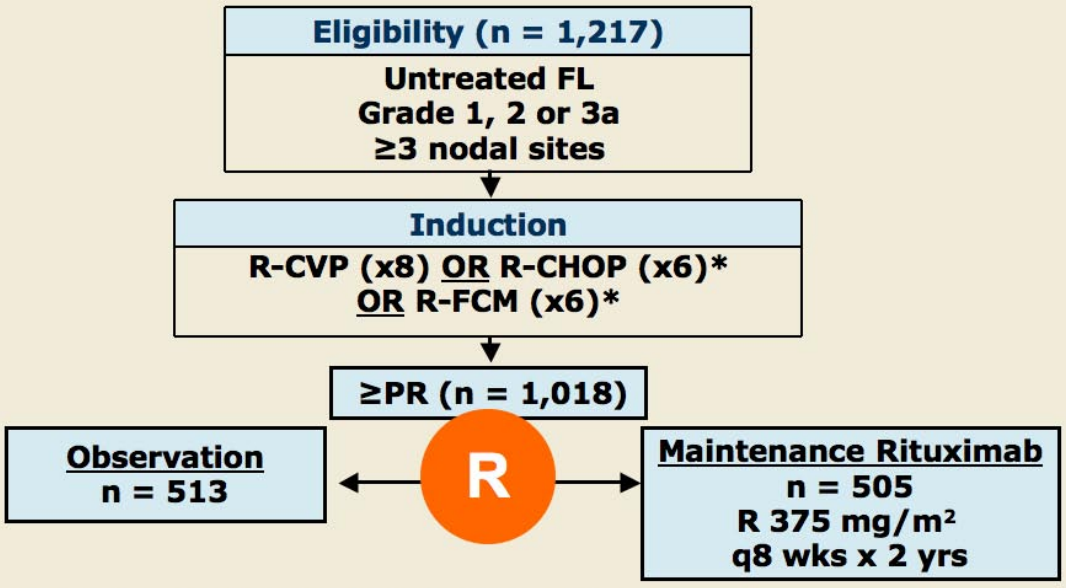


Introduction

- Rituximab (R) maintenance has shown clinical benefit for patients with follicular lymphoma (FL):
  - In the relapsed setting after induction with chemotherapy alone or chemotherapy plus R (*J Clin Oncol* 2010;28:2853).
  - In the first-line setting after induction chemotherapy alone[1] or R alone[2] ([1] *J Clin Oncol* 2009;27:1607, [2] *Blood* 2004;103:4416).
- The role of R maintenance in FL after first-line R-chemotherapy induction remains unknown.
- **Current study objective:**
  - Assess the benefit of R maintenance over the course of two years for patients with FL responding to first-line R-chemotherapy induction.

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

PRIMA Study Design



* Followed by two additional R infusions (for a total of R x 8)

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

Primary Endpoint: Progression-Free Survival

	Observation n = 513	R Maintenance n = 505
2-yr progression-free survival (PFS)	66%	82%
Hazard ratio (95% CI)	0.50 (0.39-64)	
p-value	<0.0001	

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

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Response Status at the End of Maintenance

	Observation n = 398	Rituximab (R) n = 389
Progressive Disease (PD)	162 (40.7%)	79 (20.3%)
Stable Disease (SD)	1 (0.3%)	0 (0%)
Partial Response (PR)	29 (7.3%)	28 (7.2%)
Complete Response (CR/CRu)	190 (47.7%)	260 (66.8%)
Response: End of Induction to End of Maintenance	**Observation**	**Rituximab**
Patients remaining in CR/CRu	153 (56%)	209 (75%)
Patients converting from PR/SD to CR/CRu	37 (30%)	49 (45%)

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

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PFS Benefits with Rituximab Maintenance Maintained Across Major Subgroups

Category	Subgroup	N	Hazard Ratio	95% CI
All	All	1,018	0.49	0.38–0.64
Age	<60 ≥60	624 394	0.45 0.59	0.33–0.62 0.39–0.90
FLIPI index	FLIPI ≤1 FLIPI = 2 FLIPI ≥3	216 370 431	0.38 0.39 0.61	0.19–0.77 0.25–0.61 0.43–0.67
Induction chemotherapy	R-CHOP R-CVP R-FCM	768 222 28	0.43 0.69 0.51	0.31–0.59 0.44–1.08 0.13–2.07
Response to induction	CR/CRu PR	721 290	0.52 0.45	0.38–0.70 0.29–0.72

Hazard ratio <1 favors rituximab maintenance.

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

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Safety During Rituximab Maintenance

	Observation n = 508	Rituximab n = 501
Any adverse event	35%	52%
Grade ≥2 infections	22%	37%
Grade 3/4 adverse events	16%	23%
Grade 3/4 neutropenia	<1%	4%
Grade 3/4 infections	<1%	4%

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

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Conclusions

- R maintenance for two years significantly improved PFS for patients with previously untreated FL who responded to induction with chemotherapy plus R.
- Benefits of R maintenance were seen in all major sub-groups.
- Consistent improvements were observed in secondary endpoints including CR, OR and time to next treatment (data not shown).
- The results of the PRIMA study provide evidence for a new standard of care for patients with FL who are in need of initial treatment.
- Data from the ongoing ECOG-E4402 (RESORT) trial will address how maintenance R compares to re-treatment with R at disease progression.

Salles GA et al. *Proc ASCO* 2010;Abstract 8004; Fisher RI. *Proc ASCO* 2010;Discussion.

Investigator comment on the PRIMA trial findings

These patients with follicular lymphoma (FL) required treatment, so it wasn't necessarily your watch-and-wait patient. Three quarters received R-CHOP, and the majority of the others received R-CVP.

Eighty-two percent of patients who received rituximab (R) maintenance were in remission at two years versus 66 percent in the observation arm. Overall survival wasn't reported, but that is always a question in FL. The toxicity was similar in the two arms, as was the quality-of-life analysis. A minor increase in Grade I and Grade II infections occurred in the maintenance arm, but no difference was apparent in serious life-threatening infections.

I will likely use maintenance therapy more than I did in the past, but I don't believe all patients need it. Certain patients like having a break from the doctor, but many prefer the idea of the security blanket of continual treatment and monitoring that maintenance therapy offers.

In the discussion, Rich Fisher argued that maintenance rituximab therapy is currently indicated following all treatment programs for patients with rituximab-sensitive FL, and I think that's a reasonable point.

Interview with John P Leonard, MD, June 28, 2010

Investigator comment on the PRIMA trial findings

As in the Gelmini trial, which compared prolonged treatment with rituximab to no further treatment after standard rituximab therapy, in the PRIMA study, there were more complete responses at the end of R maintenance. The concepts behind immune therapy are that it takes time to kill the last tumor cell and that the drug continues to work with time. It's important to know that more responses occur as patients continue to receive treatment.

I think R maintenance in FL will be embraced by most clinicians. In Dr Richard Fisher's discussion, he was quite positive, and although we do need to wait for more follow-up to determine whether long-term complications occur, I do think R maintenance is here to stay.

It's interesting that Dr Mathias Rummel's new trial in Germany is comparing bendamustine/rituximab (BR) with either two or four years of R maintenance, so we're not going to get away from R maintenance in low-grade lymphomas.

Interview with Stephanie A Gregory, MD, June 18, 2010

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Investigator comment on the PRIMA trial findings

I was surprised by the clear evidence favoring maintenance therapy, and the difference was clinically relevant and obviously highly statistically significant. It was a bit of a surprise for me that the results were so clear. The magnitude of difference was much greater than I expected.

In Germany — as in the US — private practitioners were already administering R maintenance off study in more than 50 percent of FL cases prior to the presentation of these data. The academic-based hospitals were saying, "We need more evidence." At this point, the PRIMA study appears quite convincing.

For more than a year, our StiL group in Germany has been accruing patients with FL to our current study, which uses the new BR backbone followed by two years versus four years of R maintenance. This trial concept is, of course, a challenge to execute, but the physicians asked for it and are highly interested in it. The study is accruing quickly and should recruit the last of 876 patients by the end of 2011. The Swiss study group is also evaluating long-term R, in this case until relapse.

Interview with Mathias J Rummel, MD, PhD, June 7, 2010

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