MANTLE CELL LYMPHOMA

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TRIAL SUMMARY: Maintenance rituximab

Gouill SL, Thieblemont C, Oberic L, et al. Rituximab maintenance after autologous stem cell transplantation prolongs survival in younger patients with mantle cell lymphoma: final results of the randomized phase 3 LyMa trial of the Lysa/Goelams Group. ASH Annual Meeting, San Diego, California, December 3-6, 2016. Abstract 145.

The LyMa trial was a phase 3, prospective randomized trial. This trial enrolled young (≤65 yr) patients with stage II or higher previously untreated mantle cell lymphoma (MCL). They received 4 cycles of R-DHAP-21 (rituximab, dexamethasone, high-dose cytarabine, platinum), followed by R-CHOP if not in complete remission (CR)/CR unconfirmed (CRu)/partial remission (PR), followed by autologous stem cell transplant (ASCT) with R-BEAM conditioning. Those who responded were randomized 1:1 to rituximab maintenance (RM) every 2 months for 3 years at standard dose, or no maintenance. A total of 249 patients were enrolled,

with a median age of 57 years (range 27 to 65). The majority were low-MIPI (Mantle Cell Lymphoma International Prognostic Index) risk (53.2%) and male (79%): 277 patients completed R-DHAP, 20 also received R-CHOP and 257 went on to ASCT; 240 were randomized to RM or no RM, with a median followup from inclusion of 54.4 months (range 52.7 to 59.2). The 4-year event free survival (EFS) was 61.4% (95% CI, 51.3–69.9) vs 78.9% (CI, 69.6–85.6) for no RM vs RM (p=0.0012), with a 54.3% risk reduction (HR, 0.457; CI, 0.28–0.74). Four-year PFS and OS were also superior in the RM arm vs. no RM: 82.2% (CI, 73.2–88.4) vs 64.6% (CI, 54.6–73; p=0.0005) and 88.7% (CI, 80.7–93.5) vs 81.4% (CI, 72.3–87.7; p=0.0413), showing a 60% reduction in risk of progression and 50% reduction in risk of death.

COMMENTARY: MCL presents at a median age of 65 years, usually with extensive disease involving lymph nodes, spleen, bone marrow, blood and gastrointestinal tract. In Canada, patients younger than 65 years usually receive intensive chemoimmunotherapy (e.g. R-CHOP/R-DHAP) followed by upfront ASCT, while older patients are usually treated with bendamustine-rituximab (BR) often followed by rituximab maintenance (RM). This may change as a recent phase 2 trial, presented at ASH and in publication, of R-BAC500 (rituximab 375 mg/m^2 day 1, bendamustine 70 mg/m^2 days 2 and 3, and cytarabine 500 mg/m^2 days 2 to 4) reported a very high CR rate of 93% and 2-year PFS rate of 81% for transplant-ineligible MCL patients 61–79 years of age (median 71). However, R-BAC500 will likely need to be proven superior to BR in a phase 3 trial before being adopted in Canada, due to the higher toxicity rates and uncertain survival benefits.[2]

Unfortunately, relapse is common within the first 3 to 4 years, and subsequent therapy is not standardized or highly effective. Ongoing efforts to improve MCL outcomes include the addition of agents to induction therapy (e.g. ibrutinib, bortezomib, cytarabine) as described, as well as the use of maintenance rituximab +/- lenalidomide.[3] Improved OS with RM for MCL was initially demonstrated vs interferon following R-CHOP chemotherapy for patients over 60 years.[4] This study formed the basis of funding for rituximab maintenance for transplant-ineligible MCL patients in Canada; however, BR has been used more often than R-CHOP following publications of the STIL1 and BRIGHT studies.[5,6] Although the MAINTAIN trial has questioned the benefit of RM following 6 cycles of BR, this study is underpowered, with only 120 randomized patients.[7] At a median followup of 54.2 months, no significant improvement in PFS was seen with RM (p=0.130), but the 95% confidence intervals were wide (HR, 0.64; 95% CI 0.36–1.14), precluding any firm conclusions from the study.

The potential role for rituximab maintenance following upfront ASCT was first shown in retrospective reports. For example, Dietrich and colleagues[8] examined 72 patients who received ASCT with (n=22) or without (n=50) RM (every 3 months for 2 years) and reported superior 2-year PFS (90% vs 65%, p=0.014) but no difference in OS. The use of RM after ASCT for MCL has been inconsistent across Canada due to lack of definitive high quality evidence. The LyMa study is, therefore, immensely important because it clearly demonstrated a PFS and OS benefit for RM after ASCT for MCL in a prospective randomized controlled trial.[1] Canadian centres will need to decide whether to adopt the RM schedule for MCL as used in the LyMa trial (every 2 months x 3 years) or the schedule commonly used for follicular lymphoma (every 3 months x 2 years). Studies of other agents as maintenance therapy, including bortezomib and ^{90}Y-ibritumomab tiuxetan, have also reported encouraging outcomes,[9,10] and lenalidomide-rituximab trials are underway. The next few years will be exciting as trials are completed that will elucidate the role of novel agents in induction and maintenance therapy for MCL.

IN BRIEF

Already known

- Mantle cell lymphoma (MCL) is a challenging disease to cure, even with aggressive upfront chemoimmunotherapy and transplantation.

What this trial showed

- In young patients with untreated MCL who achieve a response to R-DHAP (+/- R-CHOP) and autologous stem cell transplant (ASCT), maintenance rituximab improves event-free survival, progression-free survival, and overall survival over observation, and is a new standard of care.

Next steps

- The role of novel agents (ibrutinib, bortezomib, lenalidomide) as part of induction or maintenance therapy for MCL will be evaluated in ongoing trials.

References

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