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Key Points From the SHINE Trial in Mantle Cell Lymphoma

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H&O Could you provide some background on mantle cell lymphoma?

JT Mantle cell lymphoma is an uncommon type of lymphoma. It represents approximately 6% of non-Hodgkin lymphoma cases. The median age of presentation is the mid 60s. The presentation can be variable. A few patients have an indolent leukemic presentation with normal levels of lactate dehydrogenase and a low level of Ki-67. For these patients, management usually consists of watch and wait. Most patients present with nodal disease, commonly at an advanced stage, which requires treatment. The disease can also be extranodal, involving the gastrointestinal and nasopharyngeal tracts.

Treatment differs according to the patient's age and comorbidities. Younger patients (<66 years) are typically able to tolerate intensive cytarabine-containing immunochemotherapy regimens, followed by autologous stem cell transplant and rituximab maintenance. These patients generally receive 4 cycles of rituximab plus dexamethasone, high-dose cytarabine, and carboplatin (R-DHAC) or rituximab plus dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP), which leads to remission in most cases. The patients then undergo transplant, followed by 3 years of rituximab maintenance. As shown in a 2017 study by Le Gouill and colleagues, these patients can expect a 4-year rate of progression-free survival (PFS) that is well over 80%, and a 4-year rate of overall survival exceeding 90%. Although longer-term follow-up from this study is needed, these 3 components—cytarabine, transplant, and rituximab maintenance—remain the standard of care for this younger patient population.

In the past decade, treatment for older patients has moved from rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) to bendamustine/rituximab followed by rituximab maintenance for 2 years. This shift was based on results of the StiL study, which demonstrated that bendamustine plus rituximab improved PFS compared with R-CHOP. Bendamustine/rituximab has been a common first-line approach for older patients. In the StiL study, however, the median PFS after bendamustine/rituximab was only 3 years. Therefore, additional rituximab maintenance is still generally favored in the older patient population, as well as in younger patients.

H&O Do patients with mantle cell lymphoma pose any particular treatment challenges?

JT To date, there is no cure for mantle cell lymphoma. Early results from trials of chimeric antigen receptor (CAR) T-cell therapy in the salvage setting are promising, but further study is needed. Patients with a high-risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score and a high Ki-67 level over 30%, as well as patients with *TP53*-mutated disease, have a particularly poor median overall survival of less than 2 years. These patients are difficult to treat. It will be interesting to see long-term outcomes for CAR T-cell therapy in this population.

H&O What prompted the SHINE trial, which evaluated ibrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma?

JT The SHINE study was driven by the short PFS of only 3 years after first-line treatment with rituximab plus chemotherapy in older patients with mantle cell lymphoma. Evaluation of the regimen of concurrent ibrutinib and immunochemotherapy was motivated by the impressive single-agent data with ibrutinib in the setting of relapsed mantle cell lymphoma, along with phase 1b data demonstrating the safety of the combination. There are some longer-term follow-up data supporting the use of ibrutinib in first relapse. There are also increasingly solid data suggesting that the use of ibrutinib in the second-line setting leads to a respectable median PFS of 2 years. The overall response rate is nearly 80%. Among patients who do respond, the median duration of response is 3 years, and the median overall survival is 5 years. The data showed meaningful long-term outcomes in the second-line setting with ibrutinib monotherapy as opposed to salvage chemotherapy. This finding was clearly an impetus to evaluate whether concurrent use would improve outcomes for patients in the first-line setting.

H&O What was the study design?

JT Designed more than 10 years ago, SHINE was a double-blind, randomized, controlled phase 3 trial involving 523 older (≥65 years) patients. Enrollment took place in 2013 and 2014. The trial compared ibrutinib plus bendamustine/rituximab vs placebo plus bendamustine/rituximab with continuous Bruton tyrosine kinase (BTK) inhibitor therapy administered during rituximab maintenance. The primary endpoint was investigator-assessed PFS.

There were more than 250 patients in each treatment arm. Their median age was 71 years. Patients in both arms were well-matched for Eastern Cooperative Oncology Group performance status and MIPI scores. The histology was fairly well-matched. In each arm, approximately 9% of patients had blastoid or pleomorphic histology. Approximately 10% of patients had the high-risk *TP53* mutation.

H&O What were the efficacy results of the SHINE trial?

JT The complete response rate was 66% in the ibrutinib arm vs 58% in the control arm (*P*=.057). The addition of ibrutinib led to a highly significant improvement in PFS, with a hazard ratio of 0.75, signifying a 25% reduction in the risk of progression or death. A key statistic from the SHINE trial is the median 6.7-year PFS with ibrutinib plus bendamustine/rituximab compared with only 4.4 years with bendamustine/rituximab alone. This 2.3-year gain in median PFS is not just statistically significant but clinically meaningful. The PFS advantage was seen across almost all subgroup analyses, with the exception of those patients with the highest-risk MIPI score, the blastoid pleomorphic morphology, and the *TP53* mutation.

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The endpoint of PFS is key for any drug registration study. For the individual patient with mantle cell lymphoma, however, arguably the more important endpoint is the time to next treatment. Ibrutinib improved the time to next treatment, with a hazard ratio of 0.48. After more than 7 years of follow-up, subsequent second-line anti-lymphoma treatment was given to only 20% of patients in the ibrutinib arm vs 40% of patients in the control arm.

H&O What types of toxicities were reported in the trial?

JT There were more toxicities in the ibrutinib arm. In particular, the rates of rash and pneumonia were 10% higher with ibrutinib. The risk/benefit analysis of continuing ibrutinib maintenance after induction therapy must be considered after a patient develops an infection, particularly in the era of COVID-19.

Atrial fibrillation was reported in 14% of the ibrutinib arm compared with 7% of the control arm. Minor bleeding occurred in just over 40% vs just over 20%, respectively. However, there was no increase in major bleeding. Second primary malignancies were equivalent in both treatment arms.

When administering ibrutinib, the treating clinicians must therefore remain alert for infections, rash, and atrial fibrillation. After more than 10 years of using ibrutinib, we are mindful of these side effects and more comfortable managing them.

H&O Were any of the results surprising?

JT It was surprising that there was no improvement in overall survival with such an impressive PFS advantage. The lack of improvement may be partly explained by the crossover design. Patients in the control arm were able to receive ibrutinib in the second-line setting. Another explanation may be the causes of death in each arm. More patients died from progressive disease in the control arm. In the ibrutinib arm, more patients died from treatment-emergent adverse events. The latter finding argues for maintaining a low threshold for stopping ibrutinib in the event of a serious infection. COVID-19 caused 3 deaths in the ibrutinib arm compared with 2 deaths in the control arm. A much larger study with longer follow-up would be necessary to show any advantage in overall survival.

H&O How might this regimen be incorporated into clinical practice?

JT Incorporation into clinical practice will be similar to that of rituximab maintenance after rituximab/bendamustine in follicular lymphoma, another low-grade lymphoma. There is a strong PFS advantage, without an overall survival advantage, when adding ibrutinib to bendamustine/rituximab in mantle cell lymphoma. I would be happy to initiate treatment with the regimen, but I would have a low threshold for stopping ibrutinib in the event of significant toxicity, especially after a patient has completed 18 months of therapy. The median duration of therapy in patients receiving ibrutinib during the SHINE study was 2 years. Most patients did not continue treatment with ibrutinib year after year.

H&O Are there any other promising areas of research?

JT We are interested in seeing the results of the many studies that are now evaluating the role of ibrutinib and the more-specific, second-generation BTK inhibitors in combination frontline therapy of mantle cell lymphoma, including in patients who are eligible for transplant. If these studies show that the second-generation inhibitors are better tolerated, then the next questions will be how to maximize the tolerability and efficacy and how to identify the optimal duration of combination therapy.

Data from studies of CAR T-cell therapy hold enormous interest for patients who develop progressive disease early after combination therapy and for patients who relapse after ibrutinib monotherapy, especially in the setting of *TP53*-mutated and poor-risk disease. It is alluring to hope that longer follow-up might show a cure for some of these patients.

Disclosure

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Suggested Readings

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