AUGMENT: Lenalidomide/Rituximab vs Placebo/Rituximab in Relapsed or Refractory Indolent Lymphoma

Leonard JP, Trneny M, Izutsu J, et al; for the AUGMENT Trial Investigators. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;38:1188-1199.

Study Overview

Objective. To compare the efficacy and safety of lenalidomide in combination with rituximab (known as the R^2 regimen) to rituximab plus placebo in patients with relapsed or refractory follicular lymphoma or marginal zone lymphoma (MZL).

Design. Phase 3, multicenter, international, placebo controlled randomized trial.

Setting and participants. 358 patients with rituximab-sensitive relapsed or refractory grade 1-3a follicular lymphoma or MZL.

Intervention. Patients were randomly assigned 1:1 to receive lenalidomide or placebo for 12 cycles plus rituximab once per week for 4 weeks in cycle 1 and day 1 of cycles 2 through 5.

Main outcome measures. The primary endpoint was progression-free survival (PFS) as determined by independent radiology reviewers using intent-to-treat analysis. Secondary end points included overall response rate, complete response rate, duration of response, overall survival, event-free survival, and time to next anti-lymphoma therapy. Time to next chemotherapy treatment and histologic transformation were exploratory endpoints. Responses were assessed by participating investigators and independent reviewers. Computed tomography or magnetic resonance imaging was used to obtain tumor measurements. Positron emission tomography was not used. Complete remissions were confirmed by bone marrow biopsy, as bone marrow involvement is exceedingly common in these lymphomas. Gastrointestinal endoscopy was performed to obtain disease status if there was involvement by lymphoma initially.

Improvement in primary and secondary endpoints as well as extrapolatory endpoints were reported in the R^2 group. Primary efficacy analyses were conducted in the intention-to-treat population primary endpoint of PFS at 1-sided $\alpha = 0.025$ level.

Main results. PFS was significantly improved for patients treated with the R^2 regimen compared to those who re-

cieved placebo plus rituximab, with a hazard ratio of 0.46 (95% confidence interval [CI], 0.34-0.62; $P < 0.001$). Median duration of PFS in the R^2 group was 39.4 months (95% CI, 22.9 months to not reached) versus 14.1 months (95% CI, 11.4 to 16.7 months) in the rituximab/placebo group. Overall response in the R^2 group was 78% (95% CI, 71%-83%) versus 53% (95% CI, 46%-61%; $P < 0.0001$) in the rituximab/placebo group, with 34% (95% CI, 27%-41%) versus 18% (95% CI, 13%-25%) of patients achieving complete remission ($P = 0.001$). There were 15 deaths in the R^2 group versus 26 deaths in the rituximab/placebo group. Overall survival data is not mature yet.

Conclusion. The R^2 regimen was superior to rituximab and placebo in relapsed or recurrent follicular lymphomas. The regimen's safety profile was acceptable, with higher events of usual and expected but manageable toxicities in the R^2 regimen compared to rituximab/placebo.

Commentary

Nearly half of non-Hodgkins lymphomas (NHLs) diagnosed in the United States are classified as indolent B-cell lymphomas.[1] Follicular lymphomas constitute about 50% of all indolent NHLs, while MZLs comprise less than 15%.[1] These slowly progressive B-cell lymphomas are currently considered treatable but have very low cure rates. Cure is primarily limited to early stage I/II disease and may be possible in less than half of patients by applying involved-field radiation therapy with curative intent.

More than two thirds of indolent lymphomas present in advanced stages (III-IV). Despite an advanced stage at presentation, initial chemoimmunotherapy can induce complete remission in nearly 60% of patients. Unfortunately, nearly all patients relapse over the next 10 years.[2] The wait-and-watch approach is a common strategy, and most patients are administered initial therapy or subsequent lines of therapy if they are symptomatic.[2] As such, for the majority of these patients, the goal of therapy is to minimize toxicities, preserve quality of life, treat symptoms, and achieve a long PFS without an attempt to cure. Following each line of therapy, patients often revert to watchful surveillance, sometimes for more than a decade. With additional subsequent lines of therapy, lymphoma tends to get more refractory to treatment.

A median survival of nearly 2 decades has been achieved in advanced follicular lymphomas[2,3] and MZL.[4] However, wide variation in overall response, duration of response, and survival is reported based on the individual risk profile.

The drug of interest in the present study by Leonard and colleagues, lenalidomide, has immunomodulatory properties and antiproliferative effects, possibly related to its binding of the E3 ligase protein cereblon and subsequent ubiquitination of the transcription factors Aiolos and Ikaros.[5] The benefits of combination lenalidomide/rituximab against follicular lymphoma in preclinical settings have been attributed to mechanisms mediated by tumor-infiltrating lymphocytes, natural killer cells, monocytes, and antibody-dependent cell-mediated toxicity.[5] The combination has now been studied in first-line and subsequent lines of therapy for follicular lymphoma and MZL.[6]

RELEVANCE, a phase 3 trial, compared the R^2 regimen in the upfront setting in advanced follicular lymphoma with rituximab and chemotherapy combination (including CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone], CVP [cyclophosphamide, vincristine, prednisone], and bendamustine).[7] Efficacy outcomes were similar between the comparators and R^2 was noninferior. MAGNIFY, a phase 3b trial involving rituximab-sensitive and rituximab-refractory patients with previously treated follicular lymphoma and MZL, demonstrated an overall response rate of 73%, complete response rate of 45%, and median PFS of 36 months in patients who received the R^2 regimen and who entered a plan to receive maintenance with rituximab.[8]

The AUGMENT trial was conducted at 97 centers in the United States and 14 Asian and European countries; it enrolled 358 patients, 82% of whom had a follicular lymphoma, between February 13, 2014 and January 26, 2017. The study was well conducted. The R^2 regimen was compared to the often used second-line therapy of rituximab alone, and 1:1 randomization was done with stratification factors of prior rituximab use, marginal versus follicular histology, and time lapse of less than or greater than 2 years since last therapy. A limitation of this study is that it selected individuals with a better prognosis, as the study patients were not rituximab refractory and 57% had received only a single prior therapy.

As observed in other R² regimen trials in follicular or marginal zone lymphomas, the most common adverse reactions (occurring in at least 20% of patients) were neutropenia, fatigue, and constipation. These were manageable with dose adjustments and interruptions, and, in the opinion of authors, did not take away from the overall benefits seen.

The authors acknowledge that a limitation of this study was a lower assessment of median PFS in both arms by investigators than by independent reviewers. The independent review committee assessed PFS for R² at 39.4 months, whereas investigators assessed it at 25.4 months. The median PFS benefit remained at 14.1 months by both methods of assessment. This may highlight the differences of radiographic measurements in a central setting versus at individual centers.

Histologic transformation to a higher-grade aggressive lymphoma occurred in 2 patients in the R² arm and 10 patients in the placebo/rituximab arm. After transformation, 1 patient in the R² arm and 6 in the placebo plus rituximab arm died. A plausible mechanism for this variation has not been provided. If confirmed across a wider population, this may be one of the most significant benefits of the R² regimen.

Applications for Clinical Practice

Therapy for relapsed and refractory indolent B-cell lymphomas continues to evolve. While chemotherapy remains an effective option, immunomodulation using non-chemotherapeutic intervention has emerged as an attractive strategy. The AUGMENT trial further solidifies adoption of the non-chemotherapy doublet option of rituximab/lenalidomide based on the premise of immunomodulation. Both the agents have been commercially available for more than a decade and are being used for other indications beyond the study population for this trial.

Based on the AUGMENT and MAGNIFY trials, lenalidomide combined with rituximab was approved by the Food and Drug Administration for use in relapsed and refractory follicular or marginal zone lymphomas soon after the AUGMENT study results were published. The recommended lenalidomide dose for both lymphomas is 20 mg once daily orally on days 1 to 21 of repeated 28-day cycles for up to 12 cycles.

The evidence from this trial has yielded what is likely to be a practice changing regimen, with R² replacing single-agent rituximab for treating follicular lymphoma in the second line or beyond. The response rates and PFS periods were slightly lower in MZL. R² offers advantages associated with a chemotherapy-free regimen and improved PFS. Also, in the AUGMENT trial the secondary and exploratory endpoints of time to next therapy, overall response rates, and overall survival rates were improved in patients treated with R².

Practitioners may choose lenalidomide plus rituximab over rituximab alone based on the AUGMENT study. When considering this regimen, several points should be kept in mind. A very careful selection of patients would be prudent, considering that the study's follow-up of less than 4 years is short for a disease with long overall survival rates. The study was not powered to compare overall survival benefit. Also, practitioners are reminded to limit the use of lenalidomide to a maximum of 12 months, with planned interruptions and 8 doses of rituximab, replicating the trial schema. Additionally, as per the clinical trial design, the regimen is not intended for rituximab-refractory patients. Patients with MZL constituted only 18% of the study, and conclusions of superiority in this subgroup were not statistically significant. Lenalidomide is not approved for other indolent B cell lymphoproliferative malignancies, such as small lymphocytic lymphoma and chronic lymphocytic leukemia. The conclusion of the published study abstract suggests acceptable use in recurrent indolent lymphomas, but no such conclusion can be made due to lack of inclusion of all indolent lymphoma subtypes in this study.

Longer-term use of lenalidomide has been associated with a marginally increased risk of secondary hematologic malignancies in patients with multiple myeloma who were prescribed lenalidomide maintenance therapy for up to 2 years following high-dose chemotherapy and autologous hematopoietic stem cell transplant.[9] Interestingly, in the AUGMENT study and other trials using lenalidomide/rituximab, no significant increase in secondary hematologic malignancies has been reported. The absence of prior myeloablative chemotherapy and a shorter duration of use (1 year) in this group of patients may be factors in why no additional risk of secondary hematologic malignancies was observed. Longer-term

follow-up may be needed to evaluate this risk.

In the R^2 arm of this study, 55% patients experienced grades 3 and 4 neutropenia. With a median age of presentation for both follicular lymphoma and MZL of over 60 years, oncologists should remain aware of this potentially fatal complication, especially in the frail, the elderly, and previously treated individuals who may have a high risk of myelosuppression. Clinicians should be prepared to rapidly adopt strategies of dose interruption, dose reduction, and growth factor use, as implemented in the trial. Of note, despite the high rates of severe neutropenia, only 3% of the participants experienced febrile neutropenia, and 71% patients in R^2 group and 61% in rituximab group completed planned protocol therapy. Growth factor use was high at 36% in the R^2 group, which may have been responsible for a lower incidence of febrile neutropenia.

Increased toxicities of tumor flare, rash, and constipation were observed in the R^2 arm. Patients with greater than grade 1 neuropathy were excluded. For those at risk of thromboembolism, prophylactic anticoagulation or antiplatelet therapy was recommended in the trial. Lenalidomide dose was reduced to 10 mg for those with creatinine clearance of 30 to 59 mL/min.

The cost-effectiveness of lenalidomide/rituximab combination has not been fully studied against a sequential approach of using rituximab and lenalidomide for a limited number of cycles. The cost of a Revlimid 10-mg pill may be over $700.[10] Costs associated with supportive care due to additional toxicities have not been quantified. For those with cost concerns or lack of insurance coverage, the R^2 regimen may be cost prohibitive without financial assistance from charities.

Indolent NHL remains mostly incurable. The R^2 approach is still not a curative one, and resources should be directed to investigate a cure for this population. Whenever feasible, participation in a clinical trial should be encouraged. Parameters have not been reported based on prognostic groups, and the study did not identify any biomarkers that may correlate with improved outcome. Perhaps a biomarker-based trial design may be most suitable in explaining the heterogeneity in follicular and marginal zone lymphomas.

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Higher Step Volume Is Associated with Lower Mortality in Older Women

Lee IM, Shiroma EJ, Kamada M, et al. Association of step volume and intensity with all-cause mortality in older women. JAMA Intern Med. 2019 May 29.

Study Overview

Objective. To evaluate the association of number of steps taken per day and stepping intensity with all-cause mortality in older women.

Design. This was a prospective cohort study of US women participating in the Women's Health Study (WHS). Participants wore an accelerometer device (ActiGraph GT3X+, ActiGraph Corp, Pensacola, FL) on the hip during waking hours for 7 consecutive days between 2011 and 2015. The accelerator data were collected at 30 Hz and aggregated into 60-second, time-stamped epochs. Data from participants who were adherent with wearing devices (defined as ≥ 10 hours/day of wear on ≥ 4 days) were used in an analysis that was conducted between 2018 and 2019. The exposure variables were defined as steps taken per day and measures of stepping intensity (ie, peak 1-minute cadence; peak 30-minute cadence; maximum 5-minute cadence; and time spent at a stepping rate of ≥ 40 steps/minute, reflecting purposeful steps).

Setting and participants. In total, 18,289 women participated in this study. Of these, 17,708 wore and returned their accelerometer devices, and data were downloaded successfully from 17,466 devices. Compliant wearers of the device (≥ 10 hours/day of wear on ≥4 days) included 16,741 participants (96% compliance rate of all downloaded device data).

Main outcome measure. All-cause mortality as ascertained through the National Death Index or confirmed by medical records and death certificates.

Main results. In this cohort of 16,741 women, average age at baseline was 72.0 ± 5.7 years (range, 62 to 101 years) and the mean step count was 5499 per day (median, 5094 steps/day) during the 7-day data capture period between 2011 and 2015. Not taking steps (0 steps/minute) accounted for 51.4% of the recorded time, incidental steps (1 to 39 steps/minute) accounted for 45.5%, and purposeful steps (≥ 40 steps/minute) accounted for 3.1%. The mean follow-up period was 4.3 years; during this time, 504 participants died. The median steps per day across quartiles were 2718 (lowest), 4363, 5905, and 8442 (highest). The corresponding quartile hazard ratios (HRs) associated with mortality adjusted for confounders were 1.00 (reference; lowest quartile), 0.59 (95% confidence interval [CI], 0.47-0.75), 0.54 (95% CI, 0.41-0.72), and 0.42 (95% CI, 0.30-0.60; highest quartile), respectively ($P<0.01$). A higher mean step count per day, up to approximately 7500 steps/day, corresponded with progressive and steady decline in mortality HRs using spline analyses. Similar results were observed using sensitivity analyses that minimized reverse causation bias. While the adjusted analysis of measures of stepping intensity showed an inverse association with mortality rates, these associations were no longer significant after accounting for steps per day. Specifically, adjusted HRs comparing highest to lowest quartile were 0.87 (95% CI, 0.68-1.11) for peak 1-minute cadence; 0.86 (95% CI, 0.65-1.13) for peak 30-minute cadence; 0.80 (95% CI, 0.62-1.05) for maximum 5-minute cadence; and 1.27 (95% CI, 0.96-1.68) for time spent at a stepping rate of ≥ 40 steps/minute.

Conclusion. Older women who took approximately 4400 steps per day had lower all-cause mortality rates during a follow-up period of 4.3 years compared to those who took approximately 2700 steps each day. Progressive reduction in mortality rates was associated with increased steps per day before leveling at about 7500 steps/day. Stepping intensity, when accounting for number of steps

taken per day, was not associated with reduction in mortality rates in older women.

Commentary

The health and mortality benefits of exercise are well recognized. The 2018 Department of Health and Human Services Physical Activity Guidelines (DHHS-PAG) recommend that adults should do at least 150 to 300 minutes of moderate-intensity aerobic physical activity per week, or 75 to 150 minutes of vigorous-intensity aerobic physical activity per week, in addition to doing muscle-strengthening activities on 2 or more days a week.[1] Importantly, the guidelines emphasize that moving more and sitting less benefit nearly everyone, and note that measures of steps as a metric of ambulation can further promote translation of research into public health recommendations for exercise interventions. Despite this recognition, there is limited information centering on the number of daily steps (step volume) and the intensity of stepping that are needed to achieve optimal health outcomes in older adults. The study reported by Lee and colleagues adds new knowledge regarding the relationship between step volume and intensity and mortality in older women.

To date, only a handful of studies conducted outside of the United States have investigated the association between mortality and objectively measured step volume as determined by pedometer or accelerometer.[2-4] While these studies observed that higher step counts are associated with lower mortality rates during follow-up periods of 5 to 10 years, their sample sizes were smaller and the study populations were different from those included in the study reported by Lee and colleagues. For example, the cohort from the United Kingdom included only men,[2] and the participants in the Australian study were considerably younger, with a mean age of 59 years.[4] In the current study, the largest of its kind thus far, it was observed that older women in the United States who take about 4400 steps a day have a lower mortality rate compared to those who take about 2700 steps a day. Moreover, the benefit of increased step volume on mortality progressively increases until plateauing at about 7500 steps per day. On the other hand, stepping intensity does not appear to lower mortality when step volume is accounted for. These results are important in that they add novel evidence that in older women, a patient population that tends to be sedentary, increased step volume (steps per day) but not stepping intensity (how quickly steps are taken) is associated with a reduction in mortality. Thus, these findings help to better characterize steps as a metric of ambulation in sedentary older adults per DHHS-PAG and add to the evidence necessary to translate this line of research into public health recommendations and programs.

While the health benefit of regular physical activity is well known and has been brought to the foreground with DDHA-PAG, only a small percentage of older adults engage in the recommended amounts and types of exercises. In other words, finding motivation to exercise is hard. Thus, identifying practical methods to facilitate behavioral change that increase and sustain physical activity in sedentary older adults would be essential to promoting health in this population. The use of wearable technologies such as fitness trackers and smartphone apps, devices that are now widely used, has shown promise for measuring and encouraging physical activity. The study by Lee and colleagues adds to this notion and further highlights the potential significance of step volume and mortality benefits in older women. Thus, future research in fitness technology should aim to integrate behavior change techniques (such as goal setting, feedback rewards, and action planning) and physical activity levels in order to improve health outcomes in older adults.[5]

In this study, the large sample size (> 16,000 participants), high compliance rate of accelerometer use (96% compliance rate), and reliable and continuous data capture (a built-in device feature) provide a large and complete dataset. This dataset, a major strength of the study, allowed the investigators to adequately control for potential confounders of physical activity, such as history of smoking, alcohol use, diet, and self-rated health, and therefore statistically minimize biases that are common in observational studies. However, some limitations inherent to the observational design are noted in this study. For instance, the observed association between step volume and mortality is correlational rather than causal, and a one-time assessment of steps taken over 7 consecutive days (ie, exposure) may not accurately reflect step volume and intensity of study participants over the span of 4.3 years of follow-up. Also, participants of WHS are predominately white, have higher socioeconomic status,

and are more physically active than a national sample in the United States; therefore, caution should be exercised when making inferences to the general population.

Applications for Clinical Practice

Increased steps taken each day, up to about 7500 steps per day, is associated with lower mortality in older women. This finding can help inform the discussion when clinicians offer physical activity recommendations to older sedentary patients.

—Fred Ko, MD

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