Combination of Ibrutinib and Rituximab Prolongs Progression-Free Survival in Waldenström Macroglobulinemia

Dimopoulos MA, Tedeschi A, Trotman J, et. al. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. N Engl J Med. 2018;378:2399-2410.

Study Overview

Objective. To evaluate the efficacy of the combination of ibrutinib plus rituximab in patients with previously untreated or recurrent and rituximab-sensitive Waldenström macroglobulinemia.

Design. International, randomized phase 3 trial.

Setting and participants. Patients from 45 sites in 9 countries were enrolled after receiving a centrally confirmed diagnosis of Waldenström macroglobulinemia that required treatment according to current guidelines.[1] Patients who were treatment-naive or had relapsed disease were eligible. Those with relapsed disease must have demonstrated response to rituximab in the past with a duration of response of at least 12 months. Patients who were rituximab resistant or those who received rituximab within the prior 12 months were excluded.

Intervention. Patients were randomized in a 1:1 fashion to receive oral ibrutinib 420 mg once daily or placebo. All patients received rituximab 375 mg/m^2 at weeks 1 to 4 and 17 to 20. Treatment was continued until disease progression or intolerable adverse effects developed. Patients were stratified according to International Prognostic Scoring System for Waldenström Macroglobulinemia (IPSS) score, number of prior therapies, and performance status. Those who received placebo were permitted to crossover to receive ibrutinib at the time of progression.

Main outcome measures. The primary outcome of this study was progression-free survival (PFS). Secondary endpoints included time to next treatment, overall survival (OS), response rate, sustained hematologic improvement, quality of life, and safety. *MYD88* and *CXCR4* mutational status were assessed on pre-treatment bone marrow specimens.

Results. 150 patients were randomized to receive ibrutinib-rituximab (75 patients) or placebo-rituximab (75 patients). The median age was 69 years, and approximately one-third of patients were over the age of 75 years; 45% were treatment-naive. Those with relapsed disease had received a median of 2 prior treatments, and 85% of these received prior rituximab. Baseline characteristics were well balanced between the 2 groups. Mutation data was available for 136 patients enrolled, and *MYD88 L265P* and *CXCR4* WHIM mutations were found in 85% and 36%, respectively. Rituximab therapy was completed in 93% of patients in the ibrutinib group and 71% in the placebo group.

After a median follow up of 26.5 months, the 30-month

Table. **30-Month PFS Rates by Mutational Status**

Genotype	30-Month PFS Rates	
	Ibrutinib-Rituximab	Placebo-Rituximab
MYD88 L265P/CXCR4 WT	86%	33%
MYD88 L265P/CXCR4 WHIM	80%	29%
MYD88 WT/*CXCR4* WT	80%	21%

PFS was 82% in the ibrutinib group and 28% in the placebo group (median not reached vs. 20.3 months; hazard ratio 0.20, 95% confidence interval [CI] 0.11-0.38). This translated into an 80% reduction in the risk of progression or death. Overall, there was a low rate of histologic transformation to diffuse large B-cell lymphoma in the study group (2 patients in ibrutinib arm and none in placebo arm). In the treatment-naive subgroup, at 24 months the PFS rate was 84% in the ibrutinib arm compared with 59% in the placebo arm. In those with recurrent disease, the 30-month PFS was 80% in the ibrutinib arm compared with 22% in the placebo arm. Analysis across different *MYD88* and *CXCR4* genotypes showed consistent rates of higher PFS with ibrutinib-rituximab (**Table**). In addition, 30-month PFS was higher with ibrutinib regardless of IPSS score.

The 30-month OS was 94% with ibrutinib and 92% with placebo. There were 30 patients in the placebo arm that crossed over to receive ibrutinib. As assessed by the independent review committee, response rates were significantly higher with ibrutinib-rituximab (overall response rate, 92% vs. 47%). The major response rate (complete response, very good partial response, or partial response) was higher in the ibrutinib arm (72% vs. 32%). Mutation status did not affect the response rate or quality of response. Among those with at least a partial response, the median duration of response was not reached in the ibrutinib group, as compared with a median duration of response of 21.2 months in the placebo group. Serum IgM response was greater and more rapid with ibrutinib compared to placebo. Furthermore, transient increases in serum IgM levels, or "IgM flare," was seen less frequently with the addition of ibrutinib (8% vs. 47%). No patient receiving ibrutinib required plasmapheresis. Hemoglobin response was seen more frequently with ibrutinib (73% vs. 41%).

Grade 3 or higher adverse events (AE) were seen in 60% of patients in each group. Hypertension (13% vs. 4%) and atrial fibrillation (12% vs. 1%) occurred more commonly in the ibrutinib group compared with placebo. Serious AEs were seen more frequently with ibrutinib compared to placebo (43% vs. 33%). Atrial fibrillation of any grade occurred in 15% of patients receiving ibrutinib; however, 27% of these patients had a history of atrial fibrillation prior to enrollment. Bleeding occurred more frequently with ibrutinib; however, the vast majority of these were grade 1 or grade 2. Major bleeding occurred in 3 patients in each arm. No fatal adverse events were noted in the ibrutinib group, while 3 patients in the placebo group experienced a fatal event. Discontinuation rates were similar in both arms (5% vs. 4%). Dose reduction of ibrutinib occurred in 13 patients.

Conclusion. The combination of ibrutinib and rituximab reduced the risk of disease progression by 80% compared with rituximab alone. This combination should be considered as a standard treatment option for patients with symptomatic Waldenström macroglobulinemia.

Commentary

Waldenström macroglobulinemia is a B-cell lymphoma characterized by infiltrating IgM producing clonal lymphoplasmacytic cells. Observation remains the preferred approach to asymptomatic patients; however, the presence of clinical symptoms including anemia, hyperviscosity, fatigue, or other constitutional symptoms should prompt initiation of therapy. Given the relative lack of large studies to define standard treatment strategies, rituximab monotherapy has frequently been used, with response rates of approximately 40% to 50%.[2,3] Complete responses to single-agent rituximab have not been reported. Ibrutinib is an oral Bruton tyrosine kinase (BTK) inhibitor that has shown high response rates in the relapsed setting in previous studies. A study

of single-agent ibrutinib in patients with relapsed disease showed overall and major response rates of 90% and 73%, respectively.[4] The 2-year PFS was 69%. Additionally, such studies have suggested higher response rates in patients with mutated *MYD88* genotype. This data led to the approval of ibrutinib for rituximab-refractory disease. In the treatment-naive setting, at least a minor response was seen in all patients (n = 30) in a small cohort treated with ibrutinib.[5]

In the reported trial, the combination of ibrutinib plus rituximab resulted in a more robust and durable response than single-agent rituximab, with significantly prolonged PFS. Of note, the response was similar for both treatment-naive and relapsed, rituximab-sensitive patients. Interestingly, a transient increase in serum IgM level was not seen in those treated with combination ibrutinib-rituximab. Improvements in PFS and response rates were independent of IPSS score. Previous studies have suggested that response to ibrutinib is related to *MYD88* and *CXCR4* mutational status. For example, in a phase 2 trial of ibrutinib in previously treated patients with symptomatic disease, major response rates for *MYD88 L265P/CXCR* WT, *MYD88 L265P/CXCR4* WHIM, and *MYD88* WT/*CXCR4* WT groups were 91%, 62%, and 29%, respectively.[4] In the current study, however, responses with ibrutinib-rituximab were seen across all genotypes at similar rates. Furthermore, PFS did not differ based on mutational status.

Similar rates of grade 3 or higher AEs were observed in each arm. Atrial fibrillation did occur in 15% of patients in the ibrutinib arm, but discontinuation rates were low. In addition, bleeding complications with ibrutinib have been increasingly recognized; however, in this cohort there did not seem to be an increased risk of major bleeding, with a vast majority of the bleeding events being grade 1 or grade 2.

Applications for Clinical Practice

The combination of ibrutinib plus rituximab represents a reasonable first-line treatment for patients with Waldenstrom macroglobulinemia. Importantly, mutational status does not appear to impact response rates and thus this combination can be considered irrespective of *MYD88* status.

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References

1. Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenström's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. *Semin Oncol.* 2003;30:116-120.
2. Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenström's macroglobulinemia with rituximab. *J Clin Oncol*. 2002;20:2327-2333.
3. Dimopoulos Ma, Alexanian R, Gika D, et al. Treatment of Waldenström's macroglobulinemia with rituximab: prognostic factors for response and progression. *Leuk Lymphoma.* 2004;45:2057-2061.
4. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. *N Engl J Med.* 2015;372:1430-1440.
5. Treon SP, Gustine J, Meid K, et al. Ibrutinib monotherapy in symptomatic, treatment-naïve patients with Waldenström macroglobulinemia. *J Clin Oncol.* 2018;36:2755-2761.

Prescription Drug Benefits and Survival in Myeloma Among Medicare Beneficiaries

Olszewski AJ, Dusetzina SB, Trivedi AN, Davidoff AJ. Prescription drug coverage and outcomes of myeloma therapy among Medicare beneficiaries. J Clin Oncol. 2018;36(28):2879-2886.

Study Overview

Objective. To investigate the relationship between prescription drug coverage, receipt of active myeloma therapy, and overall survival (OS) among Medicare beneficiaries with multiple myeloma.

Design. Case-control and retrospective cohort archival data research.

Setting and participants. Authors examined SEER-Medicare registry and extracted patients with

histologically confirmed multiple myeloma diagnosed in the period 2006 to 2011. Availability of complete Medicare part A/B claims from 1 year before diagnosis until December 2013 was required for analysis. Patients with Medicare advantage or managed care plans did not have claims data available and hence were excluded. Beneficiaries with a diagnosis of diffuse large B-cell lymphoma (DLBCL), who typically receive parenteral drugs for lymphoma therapy, were used as a control cohort.

Main outcome measures. Association between prescription drug coverage status and OS was the primary outcome measure of interest. Authors reported 3-year restricted survival time (RMST) ratios to compare OS among the beneficiaries with different prescription drug coverages. Receipt of active myeloma therapy among beneficiaries was also studied. Relative risk, adjusting for patient and disease-related characteristics, was reported to examine receipt of active myeloma therapy.

Results. Records of 9755 Medicare beneficiaries were evaluated. Of these, 1460 (15%) had no prescription coverage at diagnosis, 3283 (34%) had part D plan prescription benefits, 3607 (37%) had sponsored prescription coverage through an employer, federal employer, or veterans plan, and 1405 (14%) had a Medicaid prescription plan. Beneficiaries without coverage had fewer comorbidities, including anemia, neuropathy, or renal disease, than those with part D prescription coverage or Medicaid. Of those without any prescription drug coverage, 41% obtained prescription plan coverage after diagnosis of myeloma by the following January. Conversely, only 19% of patients with DLBCL and no coverage obtained a prescription plan.

Patients with myeloma were followed for 4.9 years and median survival was 2.3 years, with a 3-year OS rate of 43.1% (95% confidence interval [CI], 42.1%-44.1%). Relative to the group without coverage, survival was 16% longer in the Medicare part D group and sponsored plan group (RMST 1.16; 95% CI, 1.12-1.21). Medicaid/Medicare dual beneficiaries had worse OS in both myeloma and DLBCL consistent with poor performance status and unfavorable baseline comorbidities. However, among patients with myeloma, Medicaid/Medicare dual beneficiaries had better survival (RMST 1.08; 95% CI, 1.03-1.13) compared to the group without coverage. There was no difference in OS for those with or without prescription drug coverage in the DLBCL cohort.

There were significant differences in treatment of myeloma based on types of prescription drug coverage. Due to increasing use of bortezomib following its approval by the U.S. Food and Drug Administration (FDA), parenteral chemotherapy use doubled from 24% to 48% from 2006 to 2011, and utility of active myeloma care increased from 88% to 91%. Medicare part D plan enrollees were 6% more likely to receive active myeloma care, and both Medicaid group and sponsored plan group beneficiaries were equally likely to receive active myeloma care compared to beneficiaries without prescription coverage. Medicaid enrollees were less likely to receive parenteral therapy.

Conclusion. Medicare beneficiaries with prescription drug coverage and multiple myeloma are more likely to receive myeloma therapy and have longer OS compared to those without prescription drug coverage.

Commentary

First-line therapy of multiple myeloma has evolved over the past 2 decades. Parenteral agents such as vincristine, adriamycin, dexamethasone, and cyclophosphamide and oral therapy with melphalan and prednisone were the mainstay of treatment in the past. In the past decade, the arrival of oral therapy using thalidomide or lenalidomide and parenteral therapy using bortezomib has increased OS in patients with myeloma. Most recently, a combination of lenalidomide, bortezomib, and dexamethasone has emerged as one of the frontline therapies of choice.[1] Incorporation of bortezomib or an oral immunomodulatory drug is almost universal in first-line therapy.

Oral antineoplastic therapy is increasingly being approved by the FDA and being utilized in the community. During the period 2016-2018, more than half the new FDA-approved oncology drugs were in oral formulation.[2] As such, access to these agents is crucial in cancer therapy. The cost of oral therapy in patients without prescription drug coverage is sometimes more than $10,000 per month, which represents a significant impediment to its adoption. Forty-three states and Washington, DC,

have enacted drug parity laws that require patients to pay no more for an oral cancer treatment than they would for an infusion. However, currently there is no such federal law, and Medicare beneficiaries must participate either through part D, state Medicaid, or a sponsored program to obtain prescription drug coverage. Despite being enrolled in part D, many beneficiaries fall into the "doughnut hole" (the requirement of Part D beneficiaries with high prescription drug expenses to pay more once the total cost of their medicines reaches a certain threshold) for prescription drugs at the time of need. From 2019 onward, enrollees will see significant, yet sometimes still insufficient, coverage benefits due to ending of the doughnut hole.[3] Only a very limited number of oral chemotherapy agents are covered through Medicare part B, and of those covered, only oral melphalan is used for myeloma.

The authors have acknowledged multiple limitations of their investigation, including possible unobserved clinical differences between beneficiaries. SEER-Medicare registry has limitations in obtaining individual level data and may not contain specific results of cytogenetics, laboratory risk markers, and response to therapy, which are important to determine overall outcome. A prospective evaluation may be more suitable to assess these variables independently or through a multivariate analysis in determining receipt of therapy on OS, although such a study is currently not feasible.

The indicator of active myeloma care was defined as 2 or more outpatient physician visits or receipt of parenteral chemotherapy. This definition is somewhat suboptimal, as often patients with myeloma are under surveillance and may not necessarily be receiving active treatment. Moreover, the exact prescription pattern of lenalidomide, the most active first-line oral therapy, could not be captured from this retrospective registry review. Therefore, definitive conclusions regarding use of lenalidomide and thalidomide and receipt of therapy in this population cannot be made.

A significant improvement in OS has been established using maintenance lenalidomide following high-dose chemotherapy and stem cell transplantation.[4] Only 5% of this study population received stem cell transplantation. This may be due to a median age of 77 years at diagnosis in the group studied, higher than the 66 to 70 years previously published.[5] Stem cell transplantation is now commonly being used even in the older population. The 3-year survival of 83% following stem cell transplantation in myeloma patients aged 75 to 84 years was nearly identical to that of the younger population.[6] Since stem cell transplantation is feasible in older Medicare beneficiaries and maintenance lenalidomide for 2 years following transplant improves survival, the option of providing maintenance therapy with oral lenalidomide must be made available to Medicare beneficiaries. Due to a very limited use of transplantation in this study, the impact of oral lenalidomide maintenance in OS cannot be judged.

Of the patients reviewed in this study, 6% had a listed diagnosis of plasmacytoma. These individuals typically are treated with radiation therapy only. It is unclear if these patients also received any systemic myeloma therapy or if they ever progressed to myeloma. Availability of prescription drug coverage may not be relevant to this group. Also, the authors reported that part D participants were less likely to receive classic cytotoxic chemotherapy. This may be somewhat irrelevant in Medicare beneficiaries with a median age of 77 years for current practice, as frontline induction with old classic cytotoxic chemotherapy is less commonly used in this population.

Investigators have appropriately recognized a lack of ability to discern whether inferior survival in the group without prescription drug coverage was the result of not receiving therapy at all or inability to receive oral immunomodulatory drugs. There would have been little reason for not proceeding to parenteral therapy. As noted, 41% of beneficiaries without coverage at diagnosis subsequently obtained coverage but continued to have significantly worse survival. Cause of death, including whether related to myeloma, was not reported. The authors suggest that early separation of survival curves could therefore be reflective of suboptimal first-line therapy that lacked oral immunomodulatory drugs. During the study period 2006-2011, first-line use of lenalidomide was common.

Median survival of patients with myeloma in this study was only 27 months. According to the American Cancer Society, in 2018 median survival for stage I myeloma has not been reached, stage II myeloma is 83 months, and stage III myeloma is 43 months. A robust and dynamic landscape in myeloma therapy prevents a clear attribu-

tion to individual agents, whether oral or parenteral, in improving OS. Thus, 3-year RMST, while appropriate for 2006-2011, may not be relevant today.

Applications for Clinical Practice

The oncology community routinely encounters difficulty in initiating therapy using oral agents rapidly after diagnosis of myeloma. The retrospective data analyzed in the current study suggests that delay in initiating or unavailability of oral agents may adversely impact OS. The common approach of initiating parenteral therapy while awaiting approvals from payers or charity programs and subsequently adding oral therapy when available has not been studied in assessing OS. The oncology community should initiate plans to obtain prescription drug coverage through either Medicare part D, Medicaid, a sponsored plan, or financial assistance charity programs as soon as possible after diagnosis of myeloma. Moreover, continuation of these prescription drug plans should be strongly considered throughout the course of myeloma, as subsequent lines of treatment will quite likely involve other active and approved oral agents, such as pomalidomide, ixazomib, and panobinostat, besides other supportive therapy.

One of the mechanisms to obtain prescription drug coverage includes enrollment in state Medicaid programs for those who are eligible. Currently, 17 states have not yet adopted Medicaid expansion under the Affordable Care Act. Expansion of Medicaid in these states could increase availability of prescription drug benefits. In this study, 15.8% of Medicare and Medicaid dual enrollees with access to oral agents at low or no cost did not receive myeloma care, slightly higher than the 13.1% with no prescription drug coverage. Lower utilization in this population may be explained based on differences in comorbidities or socioeconomic conditions rather than availability of a prescription plan.

The incidence of myeloma is expected to be higher in Medicare beneficiaries, and according to one estimate, in 2030 and beyond nearly 75% of diagnosed myeloma patients will be aged 64 to 84 years, an increase from nearly 66% today.[7] Changing demographics, increasing oral therapy options, and patient convenience demand attention to providing prescription drug coverage to all Medicare beneficiaries. This study lends support to that demand.

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References

1. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomized, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519-527.
2. U.S. Food and Drug Administration. Hematology/Oncology (Cancer) Approvals & Safety Notifications. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Accessed October 11, 2018.
3. Dusetzina SB, Keating NL. Mind the gap: Why closing the doughnut hole is insufficient for increasing Medicare beneficiary access to oral chemotherapy. *J Clin Oncol.* 2016;34:375-380.
4. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. *J Clin Oncol*. 2017;35:3279-3289.
5. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003;78:21–33.
6. Dong N, McKiernan P, Samuel D, et al. Autologous stem cell transplantation in multiple myeloma patients over age 75 [abstract]. *J Clin Oncol*. 2018;36(suppl): 8025.
7. Rosenberg PS, Barker KA, Anderson WF. Future distribution of multiple myeloma in the United States by sex, age, and race/ethnicity. *Blood*. 2015;125:410–412.