Enzalutamide Improves Progression-Free and Overall Survival in Metastatic Hormone-Sensitive Prostate Cancer

Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med. 2019 June 2.

Study Overview

Objective. To evaluate the efficacy of enzalutamide compared with standard first-line testosterone suppression in men with newly diagnosed metastatic, castrate-sensitive prostate cancer.

Design. Multinational, open-label, randomized phase 3 trial.

Setting and participants. 1125 men were randomly assigned to receive enzalutamide (563 patients) or standard care (562 patients) from March 2014 through March 2017. Eligible patients had a histologic diagnosis of prostate adenocarcinoma with metastases documented by conventional imaging with computed tomography (CT) and/or technetium-99 bone scan. Prior use of adjuvant testosterone suppression was allowed for up to 2 years, provided this had been completed at least 12 months prior to enrollment.

Intervention. Patients were randomized in a 1:1 fashion to receive enzalutamide 160 mg daily or nonsteroidal antiandrogen therapy with bicalutamide, nilutamide, or flutamide. All patients received testosterone suppression with goserelin, leuprolide, or degarelix. Therapy was continued until disease progression or intolerable adverse effects occurred. In November 2014 the protocol was amended to allow for early administration of docetaxel 75 mg/m^2 every 3 weeks for 6 cycles and androgen suppression. Patients were stratified according to having received docetaxel prior to randomization. This amendment was based on evidence of improved survival noted with this combination, and the decision to add docetaxel was up to the treating physician. The randomization was further stratified by disease volume, the use of bone-modifying agents, and comorbidity scores. High-volume disease was defined as the presence of visceral metastases or at least 4 bone lesions, with at least 1 being in the appendicular skeleton.

Main outcome measures. The primary endpoint was overall survival (OS). The secondary endpoints were prostate-specific antigen (PSA) progression-free survival (PFS), clinical PFS, death from any cause, or the last known follow-up PSA. PSA progression was defined as an increase in PSA level from the nadir value by ≥ 25% and by ≥ 2 ng/mL.

Main results. The baseline characteristics were well balanced between the treatment arms. High-volume disease was present in 52% of patients. Early docetaxel was planned in 45% of patients; however, 22 patients in whom docetaxel treatment was planned did not receive it. All 6 cycles of docetaxel were given to 159 patients in the enzalutamide group and 181 patients in the standard-care group. After a median follow-up of 34 months, there were 102 deaths in the enzalutamide group and 143 deaths in the standard-care group, with a hazard ratio (HR) for death of 0.67 (95% confidence interval [CI], 0.52-0.86; $P = 0.002$). Early docetaxel treatment, volume of disease, and use of bone-modifying agents did not affect this outcome. At 3 years, the OS was 80% in the enzalutamide group and 72% in the standard-care group. The rate of PSA-determined PFS was higher in the enzalutamide group compared with the standard group (3-year event-free survival, 67% and 37%, respectively), with a HR of 0.39 (95% CI, 0.33-0.47; $P < 0.001$). There were fewer clinical PFS events in the enzalutamide group (167 events vs 320 events), with a HR of 0.40 (95% CI, 0.33-0.49; $P < 0.001$). Analysis of the stratified subgroups showed the effect on OS was diminished in those with use of bone-modifying agents, those with high-volume disease, and those who received early docetaxel. The clinical PFS benefit was maintained across all subgroups, albeit with a smaller effect in those with high-volume disease and in those with early docetaxel treatment.

Treatment discontinuation for reasons other than progressive disease occurred in 12% of those in the enzalutamide group and 19% of those in the standard-care group. Overall, the adverse events were consistent with the known safety profiles of the treatment regimen. Seizures occurred in 7 patients on enzalutamide and no patients in the standard-care group. Fatigue was more common with enzalutamide.

Conclusion. Enzalutamide treatment was associated with significantly longer PFS and OS compared with standard care in men with metastatic, hormone-sensitive prostate cancer receiving testosterone suppression.

Commentary

The current study shows that the addition of enzalutamide to standard androgen deprivation therapy (ADT) improves OS and PFS in men with newly diagnosed metastatic, hormone-sensitive prostate cancer. Until recently, antiandrogen therapy had been the standard of care for these men; however, with the advent of novel antiandrogen agents, outcomes in men with metastatic prostate cancer in both the androgen-sensitive and castrate-resistant settings have steadily improved.[1-5] In the castrate-resistant setting, enzalutamide has previously been shown to improve survival in chemotherapy-naïve patients and those previously exposed to docetaxel chemotherapy.[5-7] Similarly, in the hormone-sensitive setting the combination of ADT with either abiraterone or chemotherapy has been shown to improve outcomes. In the phase 3 LATITUDE and STAMPEDE trials, the combination of abiraterone plus prednisone and ADT resulted in a 30% and 37% improvement in OS, respectively.[1,2] Six cycles of docetaxel in combination with ADT also resulted in a 37% increase in OS in those with high-volume metastatic disease.[3]

The current study adds to the growing body of literature suggesting that combination therapy in the upfront, hormone-sensitive setting improves outcomes. In the CHAARTED trial, the combination of docetaxel and ADT improved survival in men with high-volume disease, but it did not seem to benefit those with lower-volume disease.[3] However, the current data suggests a survival advantage with enzalutamide with low-volume disease as well. The use of docetaxel was similar between the 2 groups, and this suggests that the benefits of enzalutamide cannot be attributed to early integration of docetaxel. It is important to note that the subgroup analysis of those who received early docetaxel showed that these patients did not experience the same survival benefit as those who did not receive docetaxel. However, this trial was not powered for this analysis, and thus it should be interpreted with caution. PFS benefit was maintained across those who received and did not receive early docetaxel. Also worth noting is the increased docetaxel-related toxicity in the combination docetaxel and enzalutamide arm of this study. The neurological toxicity of enzalutamide was again noted, with 7 seizure events documented in this study.

Because this report on the ENZAMET study is an interim analysis, it will be important to follow these outcomes as the data set matures to ensure these effects are maintained over time. Additionally, it will be important

to see what implications the addition of enzalutamide have on quality of life measures, as these data have not yet been published.

Applications for Clinical Practice

The ENZAMET study provides evidence that in men with metastatic, hormone-sensitive prostate cancer receiving ADT, the addition of enzalutamide improves PFS and OS. In men who received early docetaxel, enzalutamide was associated with increased toxicity. Additionally, while PFS was improved in men who received enzalutamide and docetaxel, OS was not improved. The neurologic toxicities of enzalutamide should be considered, particularly in those with a prior history of seizure disorders. Based on these data, enzalutamide in combination with ADT represents a reasonable treatment option in men with metastatic, hormone-sensitive prostate cancer.

—Daniel Isaac, DO, MS

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Receipt of Primary Care Linked to High-Value Care, Better Health Care Experience

Levine DM, Landon BE, Linder JA. Quality and experience of outpatient care in the United States for adults with or without primary care. JAMA Intern Med. 2019;179:363-372.

Study Overview

Objective. To examine whether receiving primary care is associated with receipt of high-value services and low-value services and quality of patient experience.

Design. Secondary data analysis of the Medical Expenditure Panel Survey, which is an annual survey of a nationally representative sample of noninstitutionalized adults in the United States aged ≥ 18 years drawn from the National Health Interview Survey. The study used data from 2012 to 2014, and during these years the survey had a response rate ranging from 49% to 65%. The survey collected data through computer-assisted personal interviews and included data on demographic characteristics, health conditions, health status, medical services utilization, medications, costs, and experience with care. Between 21,905 and 26,509 respondents were surveyed each year.

To define whether a respondent received primary care, respondents were asked if they have a "usual source of care" and to provide the name of a physician they usually visit if they "are sick or need advice" about their health. Four additional questions asked respondents if they would visit their usual source of care for (1) "new health problems," (2) "preventive health care such as general checkups, examinations, and immunizations," (3) "ongoing health problems," and (4) "referrals to other health professionals when needed." These questions were intended to reflect the essential functions of primary care: providing first contact care that is comprehensive, continuous, and

coordinated. Any respondents who indicated that they did not have a usual source of care or answered no to any of the 4 questions were considered to not have primary care. Among respondents who identified a usual source of care, 95% met criteria for having primary care.

Setting and participants. The study included 49,286 US adults with primary care and 21,133 US adults without primary care. The average age was 50 years (95% confidence interval [CI], 50-51) among those with primary care and 38 years (95% CI, 38-39) among those without primary care. Among those who had primary care, 55% were female, 50% were non-Hispanic white, 32% Hispanic, and 13% black; among those without primary care, 43% were female, 43% were non-Hispanic white, 35% Hispanic, and 13% black. Among respondents with primary care, 58% considered their health status to be excellent or very good, as compared with 66% of respondents without primary care. Lack of insurance was reported by 7% of respondents with primary care and 34% of respondents without primary care. Chronic disease was reported in 78% of respondents without primary care, as compared with 42% of respondents with primary care. The study uses propensity score matching methods to produce a matched cohort, taking into account potential confounders. The matching procedure resulted in a final sample of 43,766 respondents with primary care matched to 17,964 respondents without primary care.

Main outcome measures. Main study outcome measures included 39 quality measures aggregated into quality composites (6 high-value services and 4 low-value services), and 7 patient care experience measures aggregated into an overall patient experience rating and 2 experience composites. High-value services are defined as delivery of services that are likely of benefit, and include the use of recommended cancer screening such as colorectal cancer screening in appropriate age groups; recommended diagnostic and preventive testing such as cholesterol measurement and influenza vaccination; recommended diabetes care such as hemoglobin A1c measurement; recommended medical treatment for medical conditions such as heart failure, coronary artery disease, and chronic obstructive pulmonary disease; and recommended counseling such as smoking cessation. Low-value services are defined as delivery of services that are considered either inappropriate or of little to no benefit, and include cancer screening in older adults; inappropriate use of antibiotics such as for bronchitis; inappropriate medical treatment such as anxiolytic, sedative, or hypnotic prescriptions for older adults; and inappropriate imaging tests for certain conditions.

Composites of underuse (high-value care) and overuse (low-value care) were constructed from each measure of high- or low-value services by identifying respondents who were eligible for the measure and determining the proportion in which recommended care was delivered (for high-value measures) or avoided (for low-value measures). Patient care experience was measured by standardized CAHPS (Consumer Assessment of Healthcare Providers and Systems) measurement for global rating of health care, doctor communication, and access to care. The patient care experience measures were dichotomized into positive responses as a rating of 8, 9, or 10 on items scored from 0 to 10, and 4 for items scored from 1 to 4. The experience composite was constructed by computing the mean for each respondent and then the mean for all respondents.

Main results. The study found that respondents with primary care were more likely to receive high-value care in 4 of 5 composite measures—cancer screening, diagnostic and preventive testing, diabetes care, and recommended counseling such as smoking cessation—but not in the composite recommended treatment for specific medical conditions such as heart failure. Respondents with primary care were more likely to receive recommended cancer screening, as compared to those without primary care (78% vs 67%, respectively, with a difference of 10.8%; 95% CI, 8.5%-13.0%). Respondents with primary care were also more likely to receive recommended diagnostic and preventive testing (with a difference of 9.9%; 95% CI, 8.7%-11.2%), to receive high-value diabetes care (with a difference of 7.8%; 95% CI, 1.2%-14.4%), and to receive counselling (with a difference of 6.9%; 95% CI, 4.1%-9.7%) when compared to respondents without primary care. However the rates of receipt of high-value medical treatments were similar among respondents with

or without primary care (with a difference of –4.6% (95% CI, –14.3% to 5.0%). In contrast, rates of low-value care were similar for those with or without primary care in 3 of 4 composites, including low-value cancer screening, medical treatment, and imaging, while those with primary care had higher rates of low-value antibiotic use (with a difference of 11.0%; 95% CI, 2.8%-19.3%). Respondents with primary care reported better patient care experience, including global rating of their health care, physician communication, and access to care, when compared to those without primary care.

Conclusion. Receipt of primary care is associated with a better patient care experience, more high-value care, and slightly more low-value care.

Commentary

Primary care has long been considered the bedrock of modern health care, and the delivery of comprehensive, continuous, high-quality primary care yields benefits to patients and the health care system.[1] Primary care is associated with better outcomes, such as lower mortality and reduced rates of potentially avoidable hospitalizations, and people living in areas with higher concentrations of primary care are more likely to report better health.[2] Primary care is also associated with reductions in health care cost and utilization while maintaining quality.[2] The current study adds to what is known about the potential benefits of primary care by directly examining the association of the use of primary care versus no primary care with outcomes of high-value care, low-value care, and patient care experience. Because this study used nationally representative data, it was able to examine adults in all age groups, not only older adults in Medicare, which prior studies have relied on.[3] The study's findings—that adults seen in primary care receive more high-value care and report better care experiences—are not surprising. The study also found that slightly more low-value care is being delivered in primary care. These findings are consistent with prior studies. Also, although primary care overall may be associated with health care benefits, there is substantial variation in the rates of overuse (of low-value care) and underuse (of high-value care) in primary care, and this may represent opportunities for improvement.[4]

This study has several limitations. Because the study defined primary care using questions that identify essential elements of primary care—first contact, comprehensiveness, continuity, and coordinated care—the findings may not apply to all individuals who have identified a primary care provider, but only to those who experience comprehensive, continuous, and coordinated care. Inclusion of all individuals who identify a usual source of primary care as the sole criteria may attenuate the association of primary care with the outcome measures. It is, however, reassuring that among those who identified a usual source of care (primary care), 95% indicated that they have care that is consistent with the principles of first contact care, comprehensiveness, continuity, and coordinated care. Another limitation is that the use of the criteria to indicate high- or low-value care may not capture the nuances of patient-centered care, preferences, or individualized decision-making that occurs in clinical care. Nonetheless, definitions used in the study for high- and low-value care are consistent with prior literature, and offer a standardized measure to indicate quality of care.

Applications for Clinical Practice

A recent trend in health care is the shift of continuity of care from primary care providers or practices to facility-based care or no continuity of care at all, and this shift disproportionately affects patients with low income and is associated with more emergency room visits.[5] The current study makes a strong case for the potential benefits of receiving primary care that is comprehensive, continuous, and coordinated, as patients in primary care are more likely to receive high-value over low-value care, and to have a better care experience. The ongoing debate on changes to the health care system and insurance options must take into account the impact of any changes on the population receiving primary care coverage, with the goal that more, rather than fewer, individuals realize the potential benefits of comprehensive primary care.

—William W. Hung, MD MPH

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Long-Term Exercise Training in Older Adults Is Associated with Reduced Injurious Falls and Fractures

de Souto Barreto P, Rolland Y, Vellas B, Maltais M. Association of long-term exercise training with risk of falls, fractures, hospitalizations, and mortality in older adults: a systematic review and meta-analysis. JAMA Intern Med. 2018 Dec 28.

Study Overview

Objective. To evaluate the association between long-term exercise interventions (duration ≥ 1 year) and risks of falls, injurious falls, multiple falls, fractures, hospitalization, and mortality in older adults.

Design. A systematic review of randomized controlled trials (RCTs) with preplanned meta-analysis was conducted to investigate the association between long-term exercise interventions and falls and fall-related adverse outcomes in adults older than 60 years. A literature search using electronic databases, including PubMed, Cochrane Central Register of Controlled Trials, SportDiscus, PsychInfo, and Ageline, was performed between February 20 and March 5, 2018. Studies selected were RCTs with exercise duration of 1 year or longer, where effects of exercise intervention were compared with a comparator group of participants aged 60 years or older. Articles were independently screened, abstracted, and assessed for risk of bias by 2 raters, who resolved divergences in data extraction and synthesis via in-person meetings.

Setting and participants. A total of 46 studies (22,709 participants; median of 203 participants per study) were included in the review and 40 studies (21,868 participants) were included in the meta-analysis. The participants' mean age was 73.1 ± 7.1 years, and 66.3% (15,054 participants) were women. Studies were mostly conducted in Europe (n = 15), North America (n = 13), and Oceania (n = 10). Multicomponent training involving multiple exercises (eg, aerobic, strength and balance; 29 RCTs) was the most common intervention modality, followed by aerobic (8 RCTs) and strength (5 RCTs) training. Exercise interventions had a mean frequency of 3 times/week, with each session lasting approximately 50 minutes, and were administered at a moderate intensity. The average compliance rate with exercise training was 65%. Comparator groups were often active controls that ranged from attention controls to more intensive interventions.

Main outcome measures. The 6 binary outcomes investigated were fallers who fell at least once, multiple times, or at least twice; fractures; hospitalization; and mortality. Estimates of outcomes were combined using risk ratios (RRs) using DerSimonian and Laird's random-effects model (Mantel-Haenszel method). Heterogeneity was evaluated using I^2 statistics, and trials with low rates of compliance (< 30%) with exercise intervention or high attrition (> 40%) were excluded in primary analyses.

Main results. Exercise training significantly reduced the risk of falls by 12% (n=20 RCTs; 4420 participants; RR, 0.88; 95% confidence interval [CI], 0.79-0.98) and injurious falls by 26% (9 RCTs; 4481 participants; RR, 0.74; 95% CI,

0.62-0.88), and reduced the risk of fractures by 16% (19 RCTs; 8410 participants; RR, 0.84; 95% CI, 0.71-1.00; $P=0.05$). Exercise training did not decrease the risk of multiple falls (13 RCTs; 3060 participants; RR, 0.86; 95% CI, 0.68-1.08), hospitalization (12 RCTs; 5639 participants; RR 0.94; 95% CI, 0.80-1.12), or mortality (29 RCTs; 11,441 participants; RR 0.96; 95% CI, 0.85-1.09). Sensitivity analyses yielded similar results, with the exception of the fixed-effect meta-analysis for the risk of fracture that showed a significant effect of long-term exercise training (RR, 0.84; 95% CI, 0.70-1.00; $P=0.047$). Meta-regression analysis on mortality and falls suggested that exercise frequency between 2 and 3 times per week was optimal and beneficial.

Conclusion. Long-term exercise training of 1 year or longer in duration is associated with a reduction in falls, injurious falls, and fractures in older adults. Moreover, moderate intensity, multicomponent exercise training performed 2 to 3 times weekly is likely safe and effective in this vulnerable population.

Commentary

Falls are exceedingly common (1 in 3 older Americans fall each year) and are the leading cause of fatal and nonfatal injuries in persons over the age of 65 years.[1,2] While fall prevention is a public health priority and a topic of interest in many research studies, there are important gaps in knowledge regarding optimal strategies to prevent falls and fall-related injuries in this high-risk population. The study reported by de Souto Barreto and colleagues provides new insights to address several of these gaps and may have a significant impact on the clinical practice of fall prevention in geriatric medicine.

Studies show that a single exercise intervention of short- to medium-term duration can prevent falls in community-dwelling older adults.[3] However, the effects of long-term exercise training (ie, intervention lasting longer than a year) on fall prevention in this population is less well characterized. This study is the first meta-analysis that aimed to evaluate the potential beneficial impact of long-term exercise training on falls and adverse fall-related outcomes in adults ≥ 60 years of age who are prone to falls. The study's findings indicate that long-term exercise training reduces the risk of falling by 12%, injurious falls by 26%, and factures by 16%. These results are important in that they add compelling evidence that exercise training of any duration can reduce falls and some fall-related adverse outcomes. Furthermore, the positive effects of long-term exercise training appear to mitigate some of the fatal and nonfatal injuries attributable to falls—the leading cause of such injuries in older adults.

The modality (type) and dose (frequency) of exercise training are important components of "exercise prescription" for older adults. However, there is a lack of research evidence to help clearly define these exercise parameters to better guide development of consensus exercise recommendations for older patients. This gap in knowledge limits the clinicians' ability to recommend evidence-based treatment regimens to older adults who are at higher risk for falls. Moreover, although exercise programs are rarely associated with serious adverse events, recent findings from the Lifestyle Interventions and Independence for Elders (LIFE) study found a modest and nonstatistically significant association between long-term, moderate-intensity physical activity programs and an increase in hospitalizations and mortality in older adults.[4,5] Taken together, these gaps in knowledge highlight the urgent need to better understand the optimal methods for administering exercise programs in older adults as well as the need for critical appraisals of the benefits and harms associated with long-term exercise training in this vulnerable population.

The results reported by de Souto Barreto and colleagues helped to address these questions. In this study, the authors found that long-term multicomponent training, particularly moderate intensity with balance exercises performed 2 to 3 times a week, appears to be a safe and effective intervention for reducing falls and injurious falls in older adults. Importantly, this type of long-term exercise regimen does not increase hospitalization and mortality, and thus supports the notion that exercise therapy is safe in older adults. Therefore, information gained from this meta-analysis should help to guide clinicians to devise a patient-centered exercise prescription for fall prevention.

The current study was well designed and has a number of strengths. The design of the systematic review and meta-analysis allowed aggregation of data from multiple trials, resulting in a more robust point estimate to evaluate

the effects of long-term exercise training on falls and fall-related outcomes that otherwise cannot be achieved with individual trials. In addition, the emphasis on long-term exercise training in older adults in the setting of falls and adverse fall-related outcomes addresses a key area of research that currently lacks a sufficient evidence base. There are also several limitations in this study, primarily due to the nature of its meta-analysis design. For instance, the study populations included in the analysis are highly heterogeneous and range from those with dementia to healthy participants. In addition, long-term exercise training, defined as a duration ≥ 1 year, was arbitrarily established as the minimum period of intervention. Thus, potential important studies that include interventions of significant duration, but less than 1 year, may not have been captured in this analysis.

Applications for Clinical Practice

Falls in older adults are common and may lead to devastating health consequences. The implementation of a long-term, multicomponent, moderate-intensity exercise regimen performed 2 to 3 times weekly can reduce falls and injurious falls in older adults.

—Fred Ko, MD, MS

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