

Solitary plasmacytoma of bone (SPB): Randomized phase III trial to evaluate treatment with adjuvant systemic treatment and zoledronic acid (ZA) versus zoledronic acid after definitive radiation treatment (Alliance A061402)

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Abstract

Solitary plasmacytoma of bone (SPB) is a localized plasma cell neoplasm associated with a substantial risk of progression to multiple myeloma (MM), yet the role of adjuvant systemic therapy following definitive radiation therapy (RT) remains undefined. We conducted a randomized phase III trial (Alliance A061402) to evaluate whether the addition of systemic therapy with ixazomib, lenalidomide, and dexamethasone (IXA-LEN-DEX) to zoledronic acid (ZA) improves outcomes compared with ZA alone in patients with SPB and minimal (< 10%) bone marrow plasma cell involvement following RT. Patients were randomized to receive six 28-day cycles of IXA-LEN-DEX-ZA or ZA alone. The primary endpoint was time to progression (TTP) to MM. The study was closed early due to poor accrual after enrolling 11 patients (IXA-LEN-DEX-ZA, n = 5; ZA, n = 6). All patients completed RT and planned treatment without dose reductions. The combination regimen was well tolerated, with limited grade ≥ 3 toxicities, including hypophosphatemia and lymphopenia. At follow-up extending beyond 4 years, the 1- and 4-year progression rates to MM in the IXA-LEN-DEX-ZA arm were 0% and 33%, respectively, compared with 37.5% and 58.3% at 1 and 2 years in the ZA-alone arm. Although underpowered, these findings demonstrate the feasibility and tolerability of an all-oral adjuvant systemic regimen in SPB and provide prospective data supporting further investigation of systemic strategies to delay progression to MM.

Introduction

Solitary plasmacytoma of bone (SPB) is a localized tumor in the bone comprised of clonal plasma cells in the absence of other diagnostic features of multiple myeloma (MM), though patients may present with < 10% clonal plasma cells in the bone marrow¹. Most patients with SPB eventually develop overt MM, and numerous factors are associated with a shorter time to progression to active MM, including the presence of high-risk cytogenetics, abnormal serum free light chain ratio, minimal marrow involvement, and high-grade angiogenesis within the plasmacytoma^{2–7}.

Localized radiation therapy (RT), given at a dose of 40–50 Gy over approximately four weeks, is the current standard of care (SOC) treatment for SPB. There have been no randomized trials assessing RT for patients with SPB. A retrospective study included of 206 patients with SPB and 52 with extramedullary plasmacytoma (EMD) reported a lower 10-year local relapse rate among those who received localized RT (12%) than those that did not receive RT (60%)⁸. Another retrospective study including 118 patients with SBP treated with RT (69 pts), systemic therapy +/- RT (44 pts), or surgical excision (5 pts) at diagnosis reported a median MM-free survival, progression-free survival (PFS), and overall survival (OS) of 112 months, 67 months, and 18.7 years, respectively⁹. An abnormal serum free light chain (sFLC) was the most significant prognostic factor, while intervention including systemic therapy was not an important prognostic factor for decreasing the likelihood of progression to active MM. The use of adjuvant chemotherapy after RT for SPB is controversial. No benefit has been noted in some studies^{10,11}, while others have concluded that adjuvant chemotherapy prolongs time to progression (TTP) to MM¹². Among the patients with SBP without bone marrow (BM) involvement or

with minimal (< 10%) BM involvement by clonal plasma cells, there is currently no consensus standard of care approach.

There is paucity of data with systemic clonal plasma cell-directed therapies in patients with SPB. Among the classes of therapies available, the proteasome inhibitor (PI) bortezomib appears to be associated with increases in total serum alkaline phosphatase and bone-specific alkaline phosphatase concentrations in patients with MM¹³. In vitro data indicate synergistic tumoricidal activity between bortezomib and lenalidomide (LEN), an immunomodulatory drug¹⁴. Ixazomib (IXA), an oral PI, appears to have a lower risk of neuropathy than bortezomib^{15,16}. Addition of IXA to a regimen of LEN and dexamethasone (DEX) is associated with a clinically meaningful improvement in PFS in transplant ineligible patients with newly diagnosed MM¹⁷ and significantly longer PFS in patients with relapsed or refractory MM¹⁸. The MRC Myeloma IX trial evaluated ZA versus clodronic acid (clodronate) in newly diagnosed transplant and non-transplant candidates and showed that ZA decreased skeletal events and prolonged OS¹⁹.

Given the established efficacy and safety of LEN combined with IXA and DEX, we conducted an adjuvant Phase III trial assessing whether the addition of LEN + IXA + DEX to ZA increases time to progression to MM (Alliance for Clinical Trials in Oncology A061402, NCT02516423). Table 1 provides the criteria for progression to MM.

The trial included a pre-registration component that allowed individuals ≥ 18 years with ECOG Performance Score 0–2 to pre-register prior to starting or after completion of RT if RT was scheduled to begin or began at most 28 days after a BM aspirate and biopsy were performed containing < 10% clonal plasma cells, respectively. Pre-registered patients were registered to the trial if the following eligibility were met: measurable disease (see Table 1) | no lytic lesions on skeletal survey or whole body PET/CT other than a singel lesion associated with SBP within 28 days prior to registration (PTReg); total radiation dose ranging from 4500 to 6000 cGy where RT was completed at most 90 days PTReg and no other treatment for SVP was administered PTReg; adequate laboratory values within 14 days PTReg (see Table 1), $QT_c < 470$ msec, and $\leq$ grade 2 peripheral neuropathy. Exclusion criteria included: another malignancy within 5 years PTReg; no prior PI or IMiD use, known gastrointestinal condition that could interfere with oral absorption or tolerance of study drug; cardiac arrhythmia, congestive heart failure, angina or myocardial infarction within 182 days PTReg.

Treatment Schedules and Trial Conduct

A stratified randomization procedure (with strata: age; percentage of abnormal plasma cells in the bone marrow; monoclonal protein/clonal light chains present in blood or urine; and minimal residual disease positivity) was used to assign participants in equal number to: Arm 1: IXA, LEN, DEX and ZA or Arm 2: ZA alone. Treatment was given in 28-day cycles for a maximum of 6 cycles where ZA was infused on day 1 of each cycle based on creatinine clearance; 4 mg IXA was administered by mouth on days 1, 8, and 15; 15 mg LEN by mouth days 1–21; and 12 mg DEX by mouth on days 1, 8, 15, and 22.

This study was monitored by the Alliance Data and Safety Monitoring Board twice yearly. Enrollment was terminated on 8/15/2019 due to poor enrollment having registered 10% of the planned 110 patients. Patients were followed for a maximum of 5 years post-registration. Here we report a summary of these patients' clinical course.

All patients provided written informed consent prior to enrollment. Participating centers received institutional review board approval, and the study was conducted in accordance with the Declaration of Helsinki. Data was collected and analyzed by the Alliance Statistics and Data Management Center team and reviewed by the study chair. All reported results are based on the study database frozen on February 9, 2023. The trial was opened at 388 study locations in the US.

Results

Thirteen patients were pre-registered to this trial from November 2016 through September 2018. Two of these patients failed to meet the eligibility criteria for registration and discontinued. The 11 patients registered to this study included five (4 male, 1 female) randomized to IXA-LEN-DEX-ZA aged 49–80 years (median: 70) and six (5 male, 1 female) randomized to ZA alone aged 44–74 years (median: 64). All patients received ≥ 40 Gy of radiation. Nine patients underwent post-radiation cytogenetics test (FISH: 8; karyotyping: 1) where none were found to have high-risk cytogenetic markers (such as t(4;14), t(14;16), t(14;20), 1q21 gain/amp, or del17p). Additional patient and disease characteristics appear in Table 2.

All 5 patients randomized to IXA-LEN-DEX-ZA completed all planned 6 cycles of treatment. No dose reductions were required. One patient omitted 3 weeks of Cycle 1 treatment due to grade 3 periorcular cellulitis. Other grade ≥ 3 toxicities reported include: grade 3 hypophosphatemia (2 pts) and grade 3 lymphocyte count decrease (1 pt) (Table 3). At the time of analysis, 2 patients were alive and without evidence of progression to MM at 4.0 and 5.1 years, respectively; 2 patients were alive at 4.8 and 4.9 years, having progressed at 4.1 and 4.8 years, respectively; and 1 patient died of unknown causes at 3.3 years, having been documented to have stable disease 2 weeks earlier. Thus, the 1- and 4-year rates of progression to MM for the IXA-LEN-DEX-ZA arm were 0% and 33% (95%CI: 0–70.0%), respectively.

All 6 patients randomized to ZA monotherapy discontinued protocol treatment due to completing all 6 planned cycles of treatment (4 pts), progression to MM (1 pt), or patient request (1 pt). No dose reductions were required. Other grade ≥ 3 toxicities reported included a grade 3 INR increase (1 pt) and grade 3 white blood cell count decrease (1 pt), considered unrelated to treatment. At the time of analysis, 3 patients were alive without progression to MM at 1.0, 2.7, and 3.7 years, respectively; 2 patients were alive at 4.8 and 4.6 years having progressed at 12 and 18 months, respectively; and 1 patient died from complications of disease progression at 2.4 years having progressed at 4.7 months. Thus, the 1- and 2-year rates of progression to MM for ZA arm were 37.5% (95%CI: 0–68.0%) and 58.3% (95%CI: 0–85.3%), respectively,

This study, prematurely closed due to limited accrual, was not able to establish the role of 6 months systemic therapy in this patient population. However, these otherwise positive data underscore the need

to further explore the safety and efficacy of oral adjuvant systemic treatment in patients with SPB, most notably in patients with minimal marrow involvement. The limited enrollment reflects the challenges posed by strict eligibility criteria and highlights the need for larger, multicenter efforts to ensure broader patient representation and in so doing, with the advantages of an all-oral approach as well as the favorable tolerability seen, meaningfully improve real-world translation to clinical practice²⁰.

Declarations

Competing Interests:

Douglas W. Sborov: Research funding: Pfizer, Johnson & Johnson, Regeneron; Consulting/Advisory: Johnson & Johnson, Sanofi, Pfizer, Bristol Myer Squibb, GlaxoSmithKline, Regeneron, Opna Bio, Legend Biotech, Arcellx

Anuj K. Mahindra: No competing financial interests.

Vera J. Suman: No competing financial interests.

Elisabet E. Manasanch: Employment/stock options: GlaxoSmithKline

Prashant Kapoor: Honorarium: Keosys; Consulting/Advisory: BeiGene, Mustang Bio, Janssen, Pharmacyclics, X4 Pharmaceuticals, Kite, Oncopeptides, Ascentage, Angitia Bio, GlaxoSmithKline, Sanofi, Abbvie; Institutional Research Funding: Amgen, Regeneron, Bristol Myers Squibb, Loxo Pharmaceuticals, Ichnos, Karyopharm, Sanofi, Abbvie, GlaxoSmithKline

Tibor Kovacsovics: Honorarium: Rigel, Servier; Consulting/Advisory: Amgen, Astellas, NeoGenomics, Rigel, Takeda

Cesar Rodriguez: Research: European Myeloma Network; Consulting/Advisory: Johnson & Johnson, Bristol Myer Squibb, Pfizer, Sanofi, Abbvie, Regeneron

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Paul Richardson: Advisory/Consulting: Bristol Myer Squibb, Celgene, GlaxoSmithKline, Karyopharm, Oncopeptides, Sanofi; Institutional Research Funding: Bristol Myer Squibb, Celgene, Karyopharm, Oncopeptides

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Tables

Tables 1 to 3 are available in the Supplementary Files section.

Supplementary Files

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