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First-Line Treatment of Multiple Myeloma with Carfilzomib, Thalidomide, and Dexamethasone: A Single-Center Report on 5 Cases from Mexico.

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Abstract

Multiple myeloma (MM) is a plasma cell malignancy in which patients usually relapse. Carfilzomib, a second-generation proteasome inhibitor, has demonstrated activity in MM in combination with thalidomide and dexamethasone (KTd) as first-line (1L) treatment. Thalidomide, due to its low cost, is one of the most common MM treatments in Latin America. Here we describe our experience with 1L KTd in 5 Mexican patients with MM. Patients received carfilzomib 20 mg/m2 in cycle 1 and 27 mg/m2 in subsequent cycles at days 1, 2, 8, 9, 15, and 16 of 28-day cycles. Thalidomide 100 mg was given orally (PO) every 24 hours from days 1 to 28 with 28-day cycles; dexamethasone 40 mg was given intravenously or PO 2 times per week every 3–4 days in 28-day cycles. Bone health management was supported with zoledronic acid 4 mg. Following KTd treatment, all patients achieved complete response or very good partial response; two patients received autologous transplants and one is undergoing pre-transplant assessment. The most frequent adverse events (AEs) were grade 1 electrolyte imbalance and grade 2 diarrhea. No AEs led to treatment discontinuation. KTd appears to be an effective and safe therapy in this Hispanic population with MM.

Key words: carfilzomib, thalidomide, dexamethasone, multiple myeloma, Mexico, Hispanic, proteasome inhibitor

Introduction

Multiple myeloma (MM) is a plasma cell neoplasia associated with a significant reduction in life expectancy.1 While the introduction of novel agents such as proteasome inhibitors and immunomodulators (IMiDs) have improved overall survival, most patients will relapse, making treatment of MM challenging.2 For patients who experience relapse after initial treatment, the duration of response decreases with each successive regimen.3 Therefore, the choice of treatment must be based on both the safety profile and effectiveness of the treatment.

The cost of health care is a major roadblock in the treatment of MM in developing countries, and availability of inexpensive therapies is vital for patients who must pay for their treatment out of pocket due to lack of access to health care institutions, or at institutions that require lower costs of treatment. Thalidomide, an IMiD used to treat MM, is one of the most widely used treatments for MM today in Latin America due to its low cost.4 The activity of thalidomide against MM has been documented since 1999, with response rates ranging from 25–75%.5,6 In addition, thalidomide with dexamethasone (Td) is the most commonly used combination therapy in Mexico7 because of its cost/benefit ratio, with an overall

response rate ranging from 41% to 63% at first-line and relapse.8,9 However, thalidomide has been associated with the development of dose-dependent peripheral neuropathy (PN), which is mainly localized to the peripheral nerves in a manner dependent on the length of the nerve fibers.10,11 In addition, the risk of side effects increases when thalidomide is used in combination with other drugs.10

Proteasome inhibition is a key strategy for managing MM, due to improvements in treatment outcomes with this therapy and the ability to combine proteasome inhibitors with other treatments such as chemotherapy and IMiDs.12 Proteasome inhibitors in combination with IMiDs currently represent the cornerstone of treatment for MM.13 Bortezomib is a first-generation proteasome inhibitor for which overall response rates of 38% and 66%, respectively, have been reported in monotherapy and in combination with dexamethasone.14,15 Bortezomib has been approved in Mexico for the treatment of MM,16 and according to recent guidelines for the treatment of MM in Mexico, bortezomib together with dexamethasone is a recommended regimen following transplantation.7 However, the development of PN limits the use of bortezomib and is associated with treatment discontinuation.17 In a randomized, open-label, phase 3 study, approximately 36% of patients treated with bortezomib monotherapy reported PN (any grade), with 7% experiencing grade ≥3 PN.14 As may be expected, PN rates are even higher with the combined regimen of bortezomib, thalidomide, and dexamethasone than with thalidomide and dexamethasone.17

Carfilzomib, a second-generation proteasome inhibitor, is a tetrapeptide of epoxyketone that, unlike bortezomib, selectively and irreversibly inhibits proteasome.18 Carfilzomib has been approved for the treatment of patients with relapsed or refractory MM (RRMM; United States, 1 or more prior lines; Mexico: at least 2 prior lines).19,20 An analysis of PN rates in 2 pivotal MM studies – ASPIRE and ENDEAVOR – found that carfilzomib is not associated with PN, and that the rate of grade ≥2 PN is lower with carfilzomib than with bortezomib.21 The phase 3 ASPIRE trial, which investigated the efficacy of carfilzomib in combination with lenalidomide and dexamethasone (KRd) in patients with relapsed MM, showed no meaningful difference in the incidence of PN between the KRd group (17.1%) and the control (Rd) group (17.0%).22 In addition, despite a baseline grade ≥2 PN incidence of 2.8%, grade ≥3 PN was 2.6% following treatment with KRd and 3.1% with Rd,22 indicating that carfilzomib did not induce PN. A safety study of 526 patients from all Phase II carfilzomib studies found that the incidence of PN was low overall (13.9%), as was the incidence of discontinuations due to adverse events.23 These studies demonstrate that carfilzomib is an effective and safe treatment option for MM.

Greater depths of response and improved outcomes in MM have been observed with multi-drug therapy, supporting a treatment paradigm shift away from two-drug combinations to more potent three- or four-drug combinations.24 Several studies have investigated triple therapy with carfilzomib, thalidomide, and dexamethasone (KTd) in patients with MM, and found that this combination is effective with low rates of PN. In a study of 91 patients with MM, first-line treatment with KTd resulted in very good partial response (VGPR) or greater in 89% of eligible transplant patients, with a rate of ≥grade 3 polyneuropathy

of 1%.25 Cardiac events of any grade were reported in 19% of patients, and ≥grade 3 events were experienced by 5%. In a phase II study of KTd as first-line treatment in newly diagnosed transplant-eligible MM patients, complete response (CR) was achieved by 64% and VGPR by 87%.26 In a meta-analysis of 13 trials that investigated carfilzomib-containing combinations for MM therapy, KTd regimens resulted in CR or greater for 21% of patients.27

Given the low cost of thalidomide, treatment regimens containing this agent are common in Mexico and other developing Latin American countries. However, to our knowledge, there have been no dedicated studies of the triplet KTd regimen in the Mexican MM population. Since we have experience with and access to thalidomide at our institute, we chose this IMiD for combination therapy with carfilzomib. By using carfilzomib in the triplet regimen (proteasome inhibitor, IMiD, and steroid), this study aimed for high response rates without the PN levels associated with the combination of bortezomib and thalidomide. Although the KTd combination was reported by a European group,25 to our knowledge there are currently no publications on its use in Hispanic populations. Here we present results from 5 Mexican patients with MM who were treated with KTd.

Case Series

Five patients from the National Cancer Institute of Mexico (INCAN) were selected for this study. These were the only 5 patients who were able to purchase the treatments, and they did not receive any other prior treatments. Patients received carfilzomib 20 mg/m2 in cycle 1 and 27 mg/m2 in subsequent cycles at days 1, 2, 8, 9, 15, and 16 of 28-day cycles. Thalidomide was given 100 mg orally (PO) every 24 hours from days 1 to 28, with 28-day cycles, and dexamethasone 40 mg PO 2 times per week was given every 3–4 days in cycles of 28 days. Notably, based on our previous experience and the literature,10 we confirm that the 100 mg/day dose of thalidomide is effective for this type of patient profile, providing a strong safety profile. Response rates were assessed every 3 months, and response definitions were based on the International Myeloma Working Group guidelines.28 Data were obtained from the central laboratory of INCAN. Bone marrow aspirate, positron emission tomography, computarized tomography, electrophoresis, and immune fixation were performed on all patients upon admission and at 6 weeks, as well as at 3, 6, 9 and 12 months. A negative MOA <Authors, can you advise what “MOA” stands for in this context?> (aspirate) needed to be confirmed and the result had to be consecutive negative. Bone health management was supported with zoledronic acid 4 mg.

Clinical response for all patients is shown in Table 1. Patient 1 was a 52-year-old female. She arrived on a gurney and was impaired (unable to walk), with spine-related bone pain, bone and skull lesions, and collapse of morphology in the T2–L5 vertebrae (Figure 1). She was diagnosed with MM in July 2015, with IgA Kappa ISS I and negative cytogenetics. Bone marrow aspirate (BMA) showed 27% plasmatic cells and lytic lesions in metastatic bone series (MBS). MRI detected fracture due to collapsed T2–L2

vertebrae. Radiotherapy treatment (RT) of 20 Gy was administered with KTd. Following induction treatment, she was provided with cementoplasty to manage painful bone metastases. Six months after treatment, she achieved VGPR. An autologous transplant was performed in July 2016. She is in maintenance with Td and showing VGPR. Grade 1 adverse events (G1 AEs) included anemia and hydroelectrolytic imbalance, and thrombocytopenia after transplant conditioning.

Patient 2 was a 56-year-old male. He arrived with bone pain and was impaired (unable to walk). He was diagnosed with MM in March 2016, with IgG Lambda ISS III, negative cytogenetics, 60% plasmatic cells, and MBS lytic lesions documented in the femur, humerus, scapula, and diseminated raindrop skull (Figure 2). Following KTd treatment, he achieved VGPR for 8 months and was subsequently assessed for autologous transplant, after which he achieved CR and received an autologous transplant. G1 AEs during induction therapy included hydroelectrolytic imbalance.

Patient 3 was a 48-year-old male. In 2013 he arrived with a jaw mass, which progressively increased in size until a biopsy found plasmatic cell neoplasia (Figure 3). He was diagnosed with MM in July 2015, with non- secretor-IgA Lambda and ISS I negative cytogenetics. He received jaw RT and KTd, achieving CR 6 months later. An autologous transplant was performed in February 2016, and he received KTd for maintenance due to inability to achieve CR post-transplant. He is currently showing VGPR. AEs included central venous catheter-related thrombosis, which occurred immediately post-transplant.

Patient 4 was a 62-year-old female. She had initial bone pain and was impaired (unable to walk), with a frontal right orbital plasmocytoma MRI detecting a fracture in lumbar region L2 on diagnosis (Figure 4). Additionally, she had a creatinine level of 6.0 mg/dl and skull plasmocytoma. She had been in remission for colon carcinoma and was diagnosed with MM in August 2015, with IgG Kappa, ISS III, negative cytogenetics. She received skull RT and KTd, and achieved CR after 6 months of treatment. She suffered a cerebral vascular event and pulmonary thromboembolism after 2 treatment cycles. She achieved VGPR 1 year post-diagnosis, after which she developed comorbid hypothyroidism and hypotension. She is currently on maintenance Td therapy. AEs included a grade 2 (G2) cerebrovascular event (brain ischemia), G2 pulmonary thromboembolism, G2 diarrhea, G2 community-acquired pneumonia, G1 hydroelectrolytic imbalance, and G1 hypotension. Of note, the hypotension was associated with hypothyroidism, as the patient had an altered dihydrotestosterone hormone panel; this hypothyroidism has been managed with levothyroxine 100 mg daily to date.

Patient 5 was a 67-year-old male. At initial assessment, he presented with eye plasmocytoma with impaired vision (Figure 5). He was diagnosed with MM in April 2015, with IgG Kappa ISS III and negative cytogenetics. At the time of diagnosis, he was recovering from a colonic carcinoma (in remission). He was not eligible for transplant, and received KTd 20 mg/m2 on days 1 and 2 of each cycle for 12 cycles, achieving VGPR at the second cycle. His plasmocytoma was reduced and continuous vision was recovered. AEs included G1 hydro-electrolyticdisequilibrium and G2 diarrhea. Although the patient

responded well to KTd and was therefore maintained on this therapy, he subsequently acquired H1N1 influenza and developed pneumonia, dying of a heart attack during his infection.

Patient 1

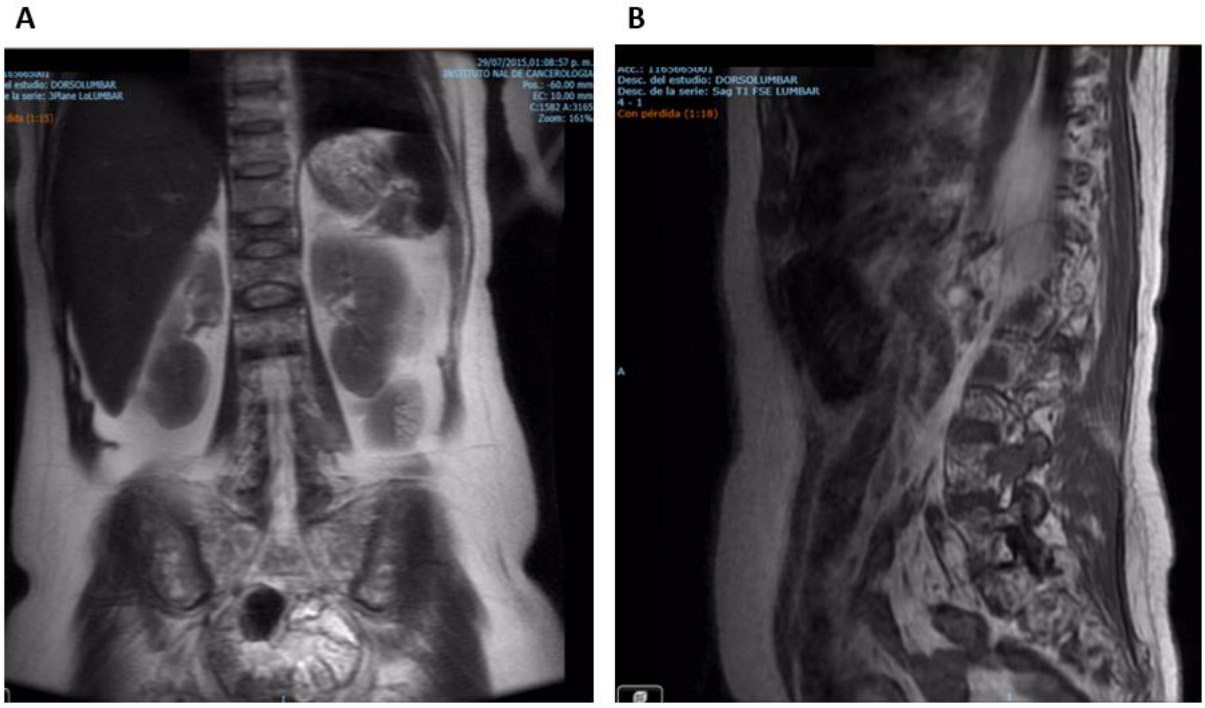

Figure 1.1. Frontal (A) and sagital (B) spine magnetic resonance for patient 1 at admission to Insitute, showing total spine infiltration and evidence of fracture and subacute colapse on T2 L2. Also shown are large mieloma activity in verteral body pedicle and in particular facets.

Patient 2

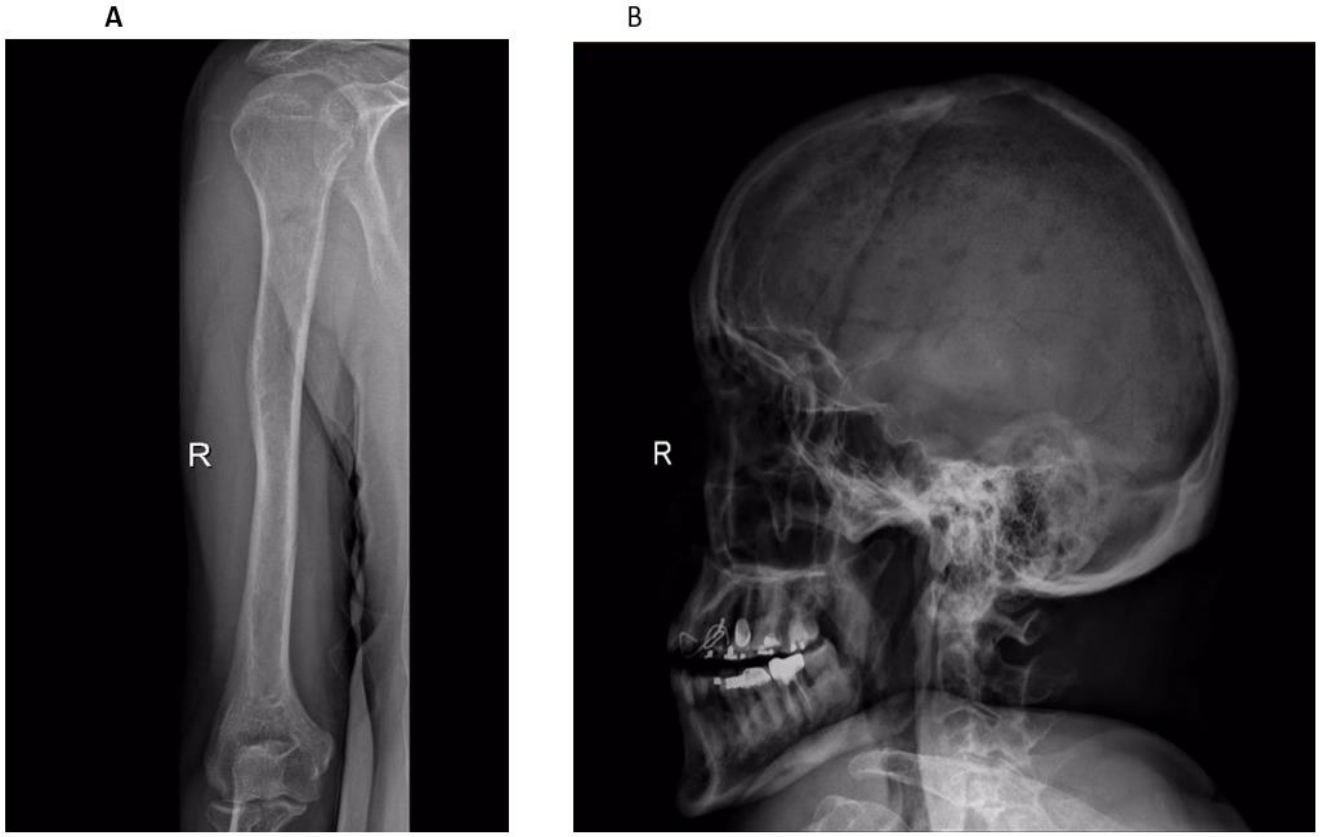

Figure 1.2. Patient 2 frontal chest radiography (A) and lateral skull (B) radiograph showing representative lytic lessions in humerus and diseminated raindrop skull lytic lessions. Images where obtained at admission to myeloma clinic.

Patient 3

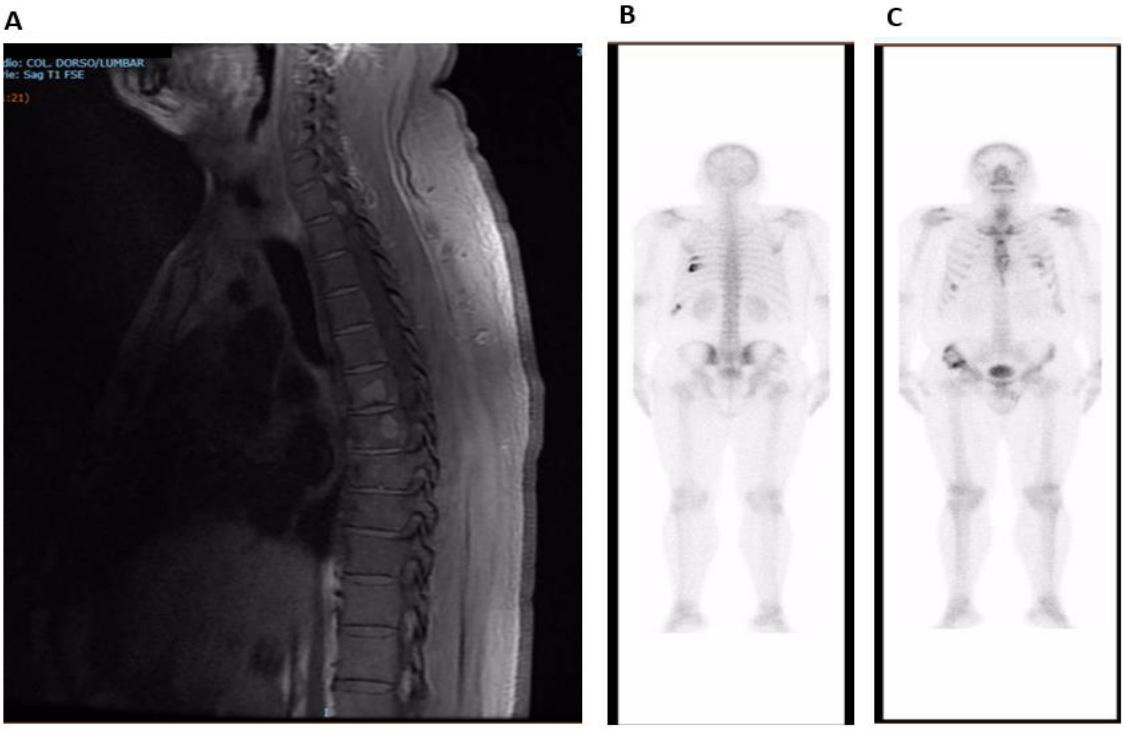

Figure 1.3 Sagital spine magnetic resonance (A) and planar bone scintigraphy (B and C) for patient 3 upon admission to institute, showing multiple hypercapturing images corresponding to multiple myeloma activity, including in jaw.

Patient 4

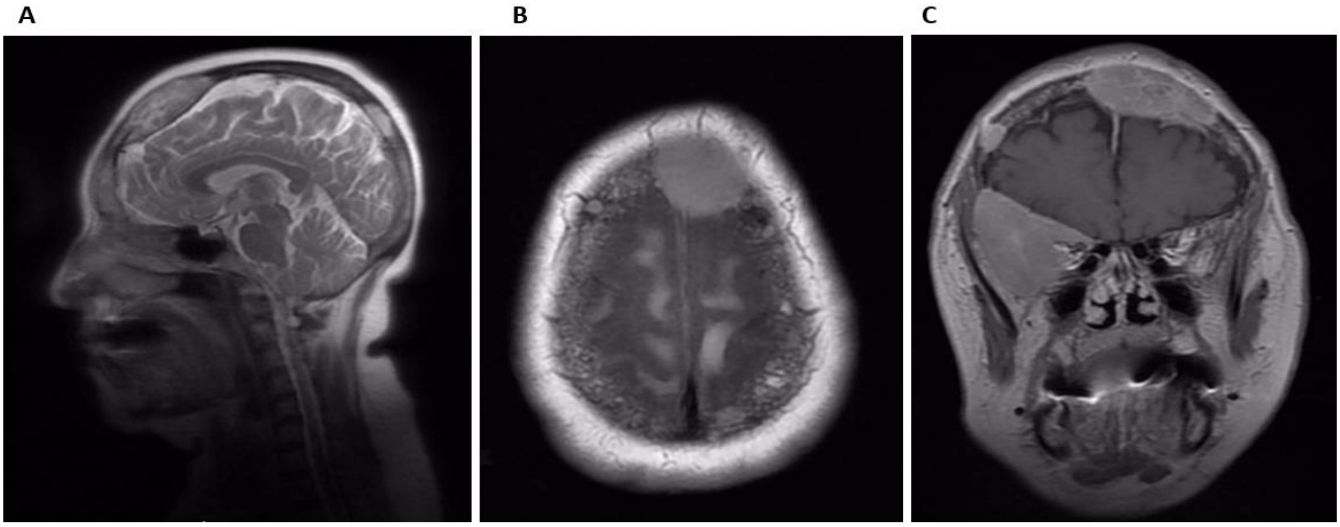

Figure 1.4 Sagittal (A), axial (B) and coronal (C) MRI showing plasmacytic plasmacytoma and multiple skull plasmocytomas in patient 4, before initiation of myeloma treatment.

Patient 5

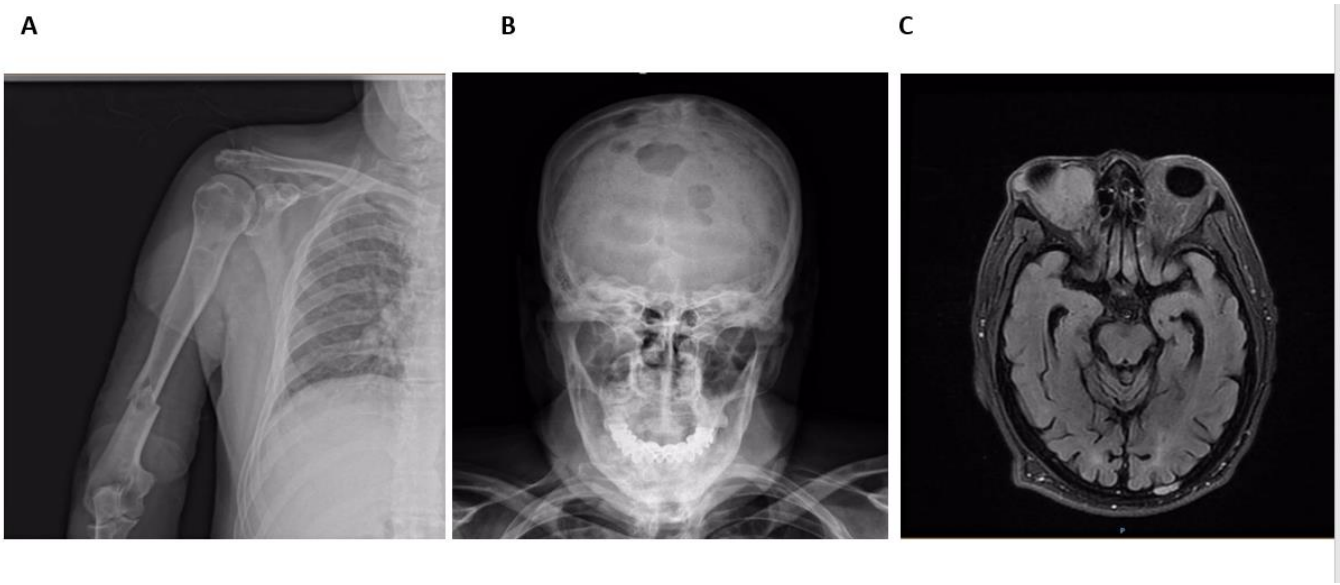

Figure 1.5, Frontal chest (A) and skull (B) radiograph and axial MRI (C) for patient 5 before initiation of treatment. The images show lytic bone and diseminated raindrop skull lytic lessions (A and B) and orbital-plasmacytoma (C).

Discussion

Few centers worldwide have explored KTd for the treatment of MM, and in Mexico, INCAN is the only center that has systematically evaluated this treatment. In this case series of Mexican patients with MM, all patients achieved CR or VGPR following treatment with KTd. Two patients received autologous transplants and one is undergoing pre-transplant assessment. Currently, the response duration is 18 months in the case with the longest follow-up time, and 6 months in the most recent case. In a previous study of KTd in MM, patients achieved a response of 89% VGPR or better (n = 91).25 In our study, all patients had some degree of response 3 months after starting treatment, and one patient managed to achieve CR at 6 months. In addition, there was no dose reduction in our study, with all patients receiving 100% of the drugs.

MM treatment is challenging because patients present with a variety of symptoms on initial presentation or at relapse. For instance, the patients in this case series had plasmacytomas, fractures, and kidney failure. Patients with MM generally arrive at INCAN at an advanced stage of disease development, and are typically impaired in wheelchairs or on a gurney. In our experience, patients arrive at this late disease stage because their physicians do not initially recognize their symptoms as being related to MM, and the patients are not referred to the appropriate specialists in a timely manner. Since diagnosis of MM is often delayed in Mexico, bone-related morbidity is high in patients. Nevertheless, we found that

KTd treatment provided the rate of response needed for patients to obtain a transplant and remain in progression-free.

Latin American countries, including Mexico, have limited financial resources to treat diseases such as MM that are in risk of relapse. Thus, it is important to seek a significant response during first-line treatment to prolong disease-free survival, as many patients will have difficulties paying for second-line treatment if the first line fails. Although hospital services are charged according to income level, patients often pay for medications out of pocket. In addition, many patients must be able to return to the work force to be able to continue paying for treatment. Whereas other triplet combinations are not affordable for the vast majority of patients in Mexico and other countries with similar economic and educational challenges, KTd has a lower cost while providing an excellent response rate and having an acceptable safety profile.

The safety profile of carfilzomib, with its lower rate of PN compared with bortezomib, makes it an attractive option for patients with relapsed MM.21,23 This is especially true for those patients with a history of PN, or who have received multiple treatments. In our case series, patients did not report PN either upon entry into the study, or following KTd treatment, which helped patients avoid additional costs associated with this side effect. In our patients, a low dose of thalidomide (100 mg/day) and a high dose of dexamethasone (40 mg, 2 times per week), the standard treatment for MM at INCAN, was used. Although thalidomide is generally given at a dose of 200 mg/day, reducing the dose to 100 mg/day results in similar efficacy with a lower rate of PN.10 In our practice, we have found that at 100 mg/day, thalidomide induces PN only after approximately 18 months of treatment or later. The decision to use dexamethasone at a 40 mg dose was based on a study that reported on the efficacy and safety of lenalidomide (25 mg for 28-day cycles) in combination with dexamethasone (40 mg for 35-day cycles).29 This is in contrast to a previous study investigating the KTd triple therapy, in which a dexamethasone dose of 20 mg was used.25 The dexamethasone dose of 40 mg did not adversely affect the safety of our combination. The most frequent AEs were G1 electrolyte imbalance and grade 2 diarrhea, followed by community-acquired pneumonia. G1 and G2 diarrhea resulted in delays in administering KTd, but none of the AEs led to suspension, dose reductions, or discontinuation of treatment.

The results achieved from the KTd regimen in this study allowed patients to become transplant candidates, a significant finding given that stem cell transplants provide patients with the best chance of prolonged survival. 30,31 Unlike allogeneic transplants, which are difficult to perform in developing countries due to economic restrictions or lack of a donor panel or suitable donor relative, autologous transplants use the patient's own stem cells and therefore do not rely on donors. Autologous transplants have been a mainstay of MM therapy for over 2 decades.30,32 Accordingly, at INCAN, MM treatment is initiated with goal of achieving VGPR or CR so that the patient can undergo autologous transplant. The cost of autologous transplant is covered by Seguro Popular, a federal program managed by the Ministry

of Health in Mexico.33 The achievement of this transplant so far in 2 of our patients was largely possible due to the efficacy and safety profile of KTd, as well as its affordable cost.

Although MM is generally described as a disease of the elderly, with a median age of onset of approximately 70 years in the United States,34 patients in our study tended to be younger when diagnosed, with an average age of 57 years. Similarly, in a retrospective analysis of patients with MM in India, the median age of diagnosis was 54 years (range, 28–84 years).35 Reasons for the younger age at diagnosis in developing countries may be related to a number of factors, including genetic risk factors, immune-mediated conditions, and early exposure to ionizing radiation, agricultural chemicals, metals, and petroleum and benzene products.35 Further studies are needed to pinpoint the potential correlation between these risk factors and MM in the Mexican patient population.

Conclusion

We propose that the KTd combination is effective and safe in a Hispanic population with MM. Our patients had excellent results, as all achieved at least VGPR at 3 months, regardless of comorbidities present at diagnosis, ISS stage, or first-line use.

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