Case study

Novel Therapy May Be the First Line Treatment for Multiple Myeloma but Should Not Be the Last Word: Two Cases Illustrated

ABSTRACT

Over the past 20 years, the treatment for multiple myeloma (MM) has evolved significantly. These pharmaceutical developments allow physicians to combine existing chemotherapy with newly approved novel and targeted medications to create various treatment regimens for MM. These novel drug combinations, immunomodulatory drugs and proteasome inhibitors, are used upfront for induction therapy as well as for maintenance and treatment of subsequent relapses. However, the emergence of resistant myeloma clones to these drugs is usually inevitable. We describe 2 cases here that demonstrate beneficial response to old traditional chemotherapy combinations after patients become resistant to all novel drugs available. Therefore, our main message is that while novel drugs should be used in frontline combinations to treat MM patients, these novel drugs should not be the last word, and often going back to the old traditional chemotherapy may illicit response and possibly prolong survival.

INTRODUCTION

Over the past 20 years, the treatment for multiple myeloma (MM) has evolved significantly. Between 1995 and 2015, ten new drugs were approved by the FDA for the treatment of MM. These pharmaceutical developments allow physicians to combine existing chemotherapy with newly approved medications to create various treatment regimens for MM. These treatment regimens, when combined with autologous stem cell

transplantation (ASCT), play an important role in significantly extending MM patients' survival (1). However, the innumerable amount of different treatment regimens does not allow for comprehensive comparisons of efficacy using phase I-III clinical trials.

In most patients, the natural history of MM includes recurrent relapses and death from resistant disease despite these new treatment options. Relapses in MM often occur after treating a heterogeneous malignant plasma cell population due to the emergence of resistant clones (2). Our two cases illustrate the story of two patients, young and old, with MM who received several different treatment regimens. The treatments included both evidence-based regimens and non-evidence based drug combinations, which delayed the emergence of a resistant clone. These two cases also raise ethical considerations regarding access to care, treatment cost, and timing of palliative care and hospice intervention.

Case 1: A 39-year-old Caucasian female presented at the age of 28 year old with worsening left lower jaw pain for approximately 7 months. She was 34 weeks pregnant at that time. She then developed swelling and numbness in June 2004 with severe pain while chewing food and was unable to open her mouth. CT scan showed a large mass starting from the ramus of the left Mandible with soft tissue extension and involvement of the left inferior alveolar nerve and evidence of pathological fracture. A biopsy of the mass revealed a plasmacytoma. Further evaluation included a bone marrow (BM) biopsy which showed 10% CD138+ plasma cells. Cytogenetics analysis was normal, while skeletal survey was normal except for the aforementioned mandibular lesion. She was treated with radiation therapy (RT), total of 4000 cGy, followed by observation (in another practice). About 8 months later, she presented with hypercalcemia and back

pain. She was diagnosed with progressive multiple myeloma IgG kappa, stage IIIA (stage II by International Staging System [ISS]), causing pathological fractures in T9, left anterior superior iliac spine and right inferior pubic ramus. Bone marrow biopsy showed 30-50% abnormal plasma cells, normal cytogenetics analysis, and monosomy 13 in 5% revealed by FISH. She was treated with 2 cycles of VAD (3) with minimal response. She was subsequently treated with one cycle of HyperCVAD part A (4), followed by peripheral blood stem cell collection and first autologous stem cell transplantation (ASCT) using conditioning regimen of melphalan 200 mg/m^2 (in middle of 2005). Three months post ASCT, repeat evaluation revealed complete morphologic and molecular remission (according to the International Myeloma Working Group criteria) (5) and patient started maintenance on phase II study using interferon alpha (IFN) 4 million units and GM-CSF 125 mcg/m^2 both given subcutaneously (SC) 3 times weekly (6). Patient became pregnant while on IFN and developed relapse manifesting with hair line fracture of her left tibia which was treated with RT 2500 cGy. She had natural delivery of healthy baby in middle of 2007. Meanwhile, she developed a left distal humerus plasmacytoma eroding the bone cortex and she underwent prophylactic internal fixation. Following that, she was started on lenalidomide (Len) and weekly dexamethasone (dexa) (Rd) (7), but had only stable disease and oral cyclophosphamide (Cy) 500 mg given weekly was added. She achieved partial response with < 5% residual plasma cells on repeat BM biopsy, but cytogenetics showed for the first time cell population with hyperdiploidy 56, XX in 3/30 metaphases and 2/30 metaphases had del 20q11.2. In 2008, about 3 years after her 1st ASCT, she had a second ASCT with high-dose melphalan 200 mg/m^2. She achieved VGPR with < 5% plasma cells in the marrow and

residual elevation of kappa at 5.05 mg/dL (normal range 0.33-1.94 mg/dL). Her cytogenetics showed 1/30 metaphases with hyperdiploidy 55, XX and del 17 and 18. After second transplant, she was on oral Cy maintenance 200 mg daily for 10 days every 4-6 wks for about 2 years. She remained stable until Aug 2010 when she developed chemical progression. She was started on Doxil, bortezomib (Bor, Velcade) and dexa (DVD) (8) for 3 cycles and then stayed on maintenance Bor (1.3 mg/m^2 SC weekly for two wks on and 1 wk off) for another 4 months when she showed chemical signs of progression and developed worsening neuropathy with pain in her legs. She was switched to a new regimen consisting of IV Cy 750 mg/m^2 and liposomal doxorubicin (Doxil) 30 mg/m^2 for one cycle and for the 2nd cycle oral etoposide 100 mg daily for 5 days was added, each cycle was given every 3 wks and continued for total of 13 cycles. The main side effect of this regimen was grade 2/3 mucositis. Chemical progression was diagnosed again in Feb 2012, and at this time, she was treated with subcutaneous Bor weekly, oral Cy 100 mg daily and dexa 20 mg weekly without response. At this point, she was admitted and given one cycle of hyperCVAD part A without significant response. Therefore, her treatment was switched to VTD-PACE (9) given in the inpatient setting for two cycles and with good response achieving VGPR. She was placed on VTD maintenance for 5 months. In Dec 2012, she showed signs of progression and was started on carfilzomib (Carf) single drug at the recommended doses per the manufacturer (Onyx Pharmaceuticals, Inc.). She had significant incremental elevation of liver enzymes after each cycle and the treatment was discontinued during the 3rd cycle, however, she responded and achieved 80% reduction in her serum free light chain which plateaued at around 13 mg/dL. Because of

the liver toxicity, she was switched to pomalidomide (Pom) 4 mg daily for 21 days every 4 wks with no response and therefore added oral Cy 200 mg daily and prednisone 80 mg daily on days 1-5 for each subsequent cycle. Five months later, markers were increasing, and she was switched to Len/Carf/dexa (See Table 1) every 28 days. This time, her liver function tests remained normal. While recovering from the 3rd cycle in Dec 2013, she developed severe neck pain and was diagnosed with a new destructive lesion in C2. She had neck brace and received 2000 cGy of RT with good clinical response. During that time, her kappa was up to 142.4 mg/dL and she was started on thalidomide (Thal) 100 mg daily and weekly dexa, and then Carf was added after RT was completed at 20 mg/m^2 days 1,2,8,9,15,16 every 4 wks for one cycle with progressive disease. She then received VBMCP (10) regimen in the outpatient setting for one cycle without response. Vorinostat was added at 200 mg daily orally for 5 days every week for the second cycle. Meanwhile, pain and swelling developed in her previously involved left humerus. Imaging showed progression with extension of her myeloma into the soft tissues. She received RT, 2000 cGy in 10 fractions, with excellent response. At this point, she was started on weekly SC Bor 1.6 mg/m^2 with vorinostat 100 mg daily (which was increased to 400 mg daily in the 2nd cycle), dexa 40 mg weekly, repeated every 3 wks. Because of lack of response, Thal 100 mg daily was added and then switched to full dose Carf with weekly dexa, daily Thal 100 mg, and vorinostat for one cycle. Now 10 and 1/2 years from diagnosis, with lack of response to the Carf combination, she was started on DT-PACE. She had good response, both symptomatically (improved bone pain) and chemically (drop in her kappa to as low as 12.31 mg/dL). The regimen was given during 6 days hospitalization every 4-5 wks with

pegfilgrastim (neulasta). The patient developed pancytopenia after each cycle and required hospitalization on 2 occasions for neutropenic fever and septicemia, including a brief trip to the intensive care unit. After the 3rd cycle, she was able to go with her 5 children and husband on an organized trip. She was given oral Thal 100 mg daily and SC interferon-alpha ($3x10^6$ units three times weekly) maintenance regimen. Upon her return, she showed chemical progression again and was admitted for another cycle of DT-PACE. She received her last cycle in Feb 2015 which was complicated by pancytopenia and bilateral pneumonia from which she recovered. The patient course from diagnosis to the end of 2014 is illustrated in Fig 1 with more than 7 chemical and clinical relapses. During all that time, she was actively taking care of the household and her five children. She had help and support from her parents and one of them always came with her each clinic visit. Over the last year of her life, she had developed significant muscle wasting and weight loss, likely from high myeloma tumor mass. Patient eventually died from her progressive disease and bilateral pneumonia almost 11 years after diagnosis. (See Table 1 for details of regimens used).

Case 2: An 80-year-old Caucasian male who was diagnosed with kappa light chain multiple myeloma stage IIIB (stage III by ISS) at the age of 74 years. He presented with anemia and fatigue and found to have acute renal failure with creatinine of 4 mg/dL. Skeletal survey showed one lesion in vertebrae L3, and cytogenetic analysis showed normal male karyotype but FISH was positive for Del 13 and IgH gene locus rearrangement. He was started on combination of Cy, Bor and dexa (CVD) (11) for 3 cycles, then proceeded to have high-dose melphalan 140 mg /m^2 and ASCT. He

achieved complete remission with improved creatinine to baseline of about 1.4 mg/dL. He was placed on oral Cy maintenance 200 mg/day X 10 days every month for 18 months, he eventually had chemical progression/relapse, and dexa 40 mg X 4 days every 2 wks was added for one cycle, followed by CVD with minimal response. He was switched to Len 15 mg (dose adjusted according to kidney function) and low dose dexa (7) and had that for 14 months, then Bor was added for 2 more cycles due to disease progression. Due to minimal response, he was started on a single agent Carf and received 15 cycles before showing signs of laboratory progression. He received one cycle of CVD without response, then changed treatment to Pom 4 mg/day for 21 days every 28 days and dexa 40 mg weekly for 6 months until he stopped responding. At this time, he was started on our modified VBMCP, which is given without Mel (VBCP, see Table 1) all in the outpatient clinic, followed by pegfilgrastim. So far, patient has received 8 cycles of VBCP, with continuous response achieving partial remission. He is supported with blood transfusions due to persistent thrombocytopenia. Again, charting his kappa light chain levels over the years (Fig 2) demonstrates lack of CR with shorter responses in the last 2.5 years. His last bone marrow biopsy was done about 14 months ago and showed 40% plasma cells by CD138 immunohistochemistry, while his cytogenetics showed 48 X,-Y and complex abnormalities in 12 metaphases including t(8;14), t(1;8), t(3;13), del 13, trisomies 11, 15, 19 and 21, as well as del 16 and 20. FISH studies showed del 13, IGH/MYC gene loci fusion, and amplification of MAF gene.

One may question quality of life considering that he is in clinic twice weekly, with the great support of his wife. He is wheel chair bound due to muscle wasting and undergoes home physical therapy. However, he otherwise enjoys his daily activities, including

reading, listening to his favorite music, and entertaining his friends in the comfort of his home. (See Table 1 for details of regimens used)

DISCUSSION

Our two cases illustrate several important points in the treatment of MM. In this report we demonstrated the use of different combinations in sequential and continuous manner to keep the patient with MM alive. It seems that the natural history of recurrent resistant relapses has not changed but rather delayed and stretched because of the various available and effective therapies. Furthermore, the treatment options used in these two cases may not be available for many myeloma patients in other Western and developing countries. Even in our own community, a patient like the ones presented here may have been referred to palliative care/Hospice earlier in the course of their disease, which may have lead earlier death. From that point of view, these cases may not be an unusual case of MM, but rather represents other similar cases with similar disease course, even in older patients, receiving this kind of sequential therapy. It is also important to think about these cases in view of the discussions in regards to the cost of all the new novel drugs and access to care. Our patients, had Medicaid/Medicare or just Medicare alone, that covered all the treatments including two ASCTs in case 1. However, allogeneic transplant, which some transplant experts consider the best next step for young MM patients like case 1, was not possible because it is not covered by Medicare. Considering that case 1 was a young mother of 5 children, then we believe that the cost per year saved may have been fully justified.

Few points emerged from these teaching cases regarding the use of the available drug combinations: 1. Both cases illustrate the use of same drugs again (such

as Cy, Bor, dexa and ASCT) in repeat cycles and at later time in the course of the disease with positive effect; 2. One can mix and match drugs at different time points in order to elicit more responses, albeit without existing evidence in the literature; 3. Old chemotherapy drug combinations, with or without novel agents, can work even when newer novel drugs stop working. Furthermore, in case #2, the VBCP served as a bridge for newer potentially less toxic therapies that were approved recently in 2015. Thus our conclusion is that while novel drugs should be used in frontline combinations to treat MM patients, these novel drugs should not be the last word, and often going back to the old traditional chemotherapy may illicit response and possibly prolong survival.

Figure Legends

Fig 1: The illustration of the time course (2004-2015) of case 1 with relapses documented in the bottom panel showing the curve for changes in serum free kappa light chain (mg/dL, Y axis) generated by EPIC medical records and demonstrating that with time (X axis), remissions became shorter and the relapses (indicated by spikes in kappa light chain) got more frequent and more resistant as illustrated (upper panel, Y axis) by the number of different regimens used. (**Abbreviations:** ASCT, autologous stem cell transplantation; IFN, interferon alpha; RT, radiation therapy; Lt, left; C2, cervical vertebra 2; T, thoracic vertebra).

Fig 2: Time course of Case 2 (2009-2016, yellow colored bar) which shows the curves for kappa (mg/dL, Y axis) and Kappa/lambda ratio as well as the different treatment given at times of disease progression. The lettered lines represent the length of different

treatments given to the patient after ASCT. The X axis shows the time line for his light chain measurements and the different treatment given. A, Cy maintenance. B, Cy +dexa. C, CVD. D, Len +dexa with and without Bor. E, Carf as single agent. F, Carf +Cy (500 mg weekly) +dexa. G, Pom +dexa. H, Pom +Bor +dexa. K, VBCP, so far 8 cycles. (**Abbreviations:** Cy, cyclophosphamide; dexa, dexamethasone; CVD, Cy +Velcade [bortezomib] +dexa; Len, lenalidomide; Carf, carfilzomib; Pom, pomalidomide; Bor, bortezomib; VBCP, vincristine +BCNU [carmustine] +Cy +Prednisone).

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252 Table 1: Details of chemotherapy regimens used in these two cases.

Regimen	Schedule of drug delivery	Frequency	Growth factor Yes/No
HyperCVAD* (inpatient)	Days1-3: Cy 300mg/m^2 IV every 12 hr (with mesna) Days 4-5: Doxorubicin 50mg/m2 & vincristine 2mg given in continuous IV for 48 hrs Days 1-5: Dexa 40mg orally	Every 28-35 days	Yes
DVD (Outpatient)	Days 1, 4, 8, and 11: Bor (V) 1.3mg/m^2 SC Day 4: Pegylated liposomal doxorubicin 30mg/m^2 IV over 60 minutes. Days 1-4: Dexa 40mg orally	Every 3 wks	No
VTD-PACE** (Inpatient)	Days 1, 4, 8, and 11: Bor 1 mg/m^2 SC Continuous: Thalidomide 50–200mg orally daily at bedtime Days 1-4: Dexa 40mg orally daily Days 1-4: Cyclophosphamide 400mg/m^2 + etoposide 40mg/m^2 + cisplatin 10mg/m^2 + doxorubicin 10mg/m^2, all given in continuous IV infusion over 24 hours daily.	Every 28-35 days	Yes
Carf/Len/Dexa	Carf 20 mg/m^2 IV on days 1,2,15, 16; Len 25 mg daily PO X 21 days; dexa 40 mg weekly.	Every 28 days	No
VBMCP (outpatient)	Day 1: vincristine 1.2mg/m^2 (limit of 2 mg) IV, BCNU 20mg/m^2 IV, Cy 400mg/m^2 IV Days 1-4: oral Mel 8mg/m^2 Days 1-7: oral prednisone 40mg/m^2	Every 35 days	Yes/No
VBCP*** (Outpatient)	Day 1: vincristine 1.2mg/m^2 (limit of 2 mg) IV, BCNU 20mg/m^2 IV Days 1-4: Cy 400mg/m^2 IV (± mesna) Days 1-7: oral prednisone 40mg/m^2	Every 28 days	Yes

CVD (outpatient)	Days 1,8,15: Cy 500mg oral or IV Days 1,4,8,11: Bor 1.3mg/m^2 SC and Dexa 40mg† on the day of and the day after Bor.	Every 21 days	No

Abbreviations: Bor. Bortezomib; Dexa, dexamethasone; Cy, cyclophosphamide; Mel, melphalan.

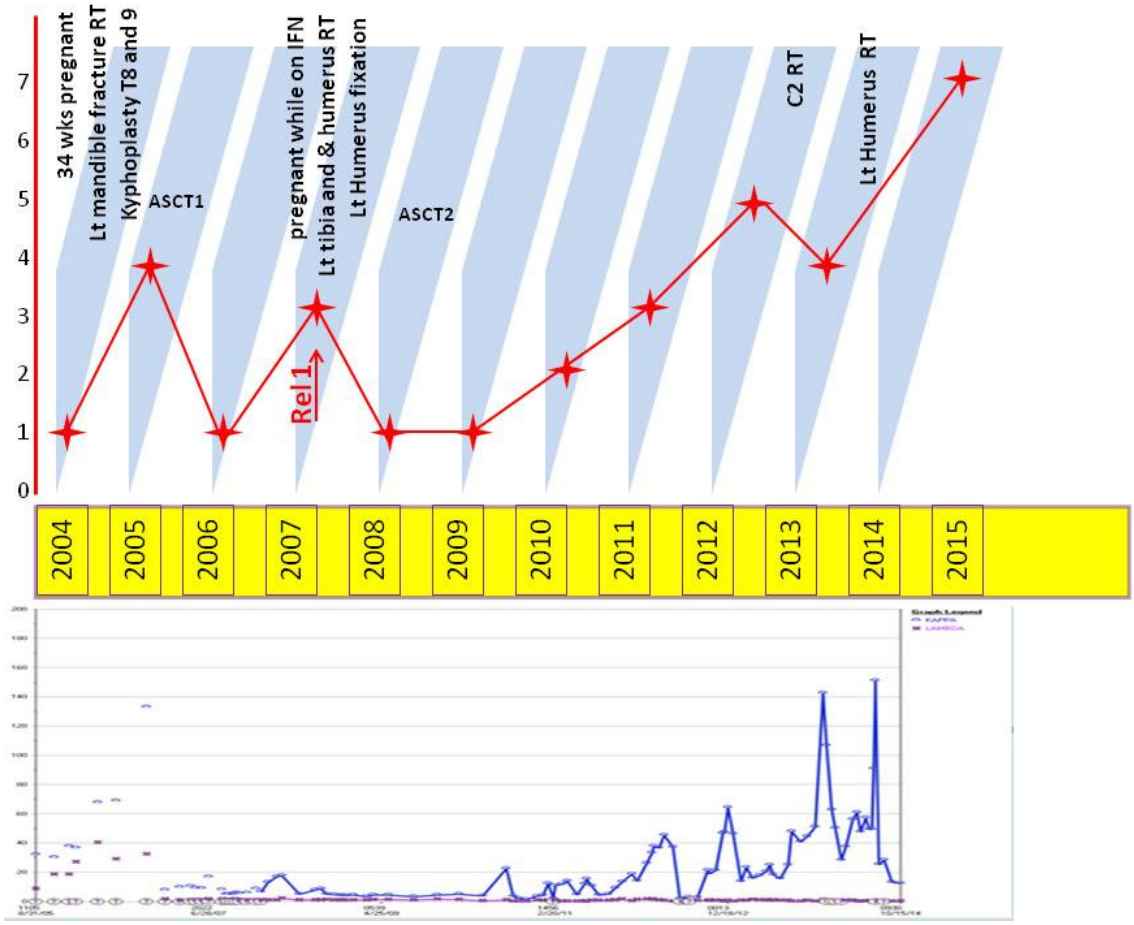
*Day 11 of this regimen was not given in our practice.

**DT-PACE is the same regimen but without Bor (Velcade). Usually days 8 and 11 are omitted in our practice.

***This regimen was developed in our practice, separate manuscript on our experience is in preparation.

† After first cycle, dose is reduced to 20 mg.

271 Figure 1.



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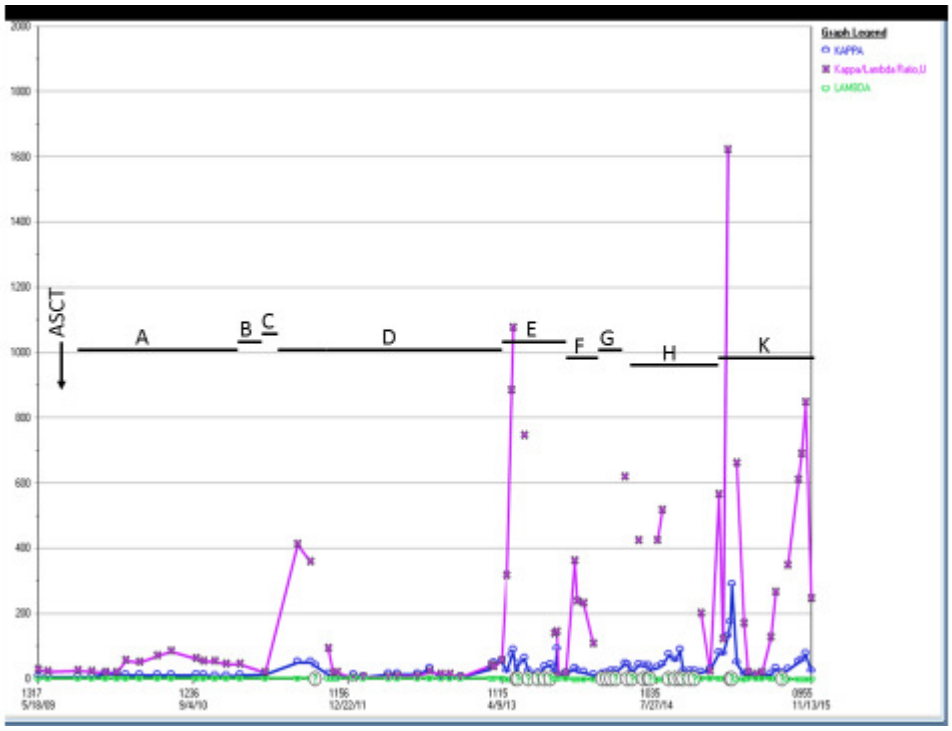
279 Figure 2.



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