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CASE REPORT

Long-term survival in multiple myeloma

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Key Clinical Message

The survival of multiple myeloma patients has improved very significantly over the last decade. Still median overall survival is inferior to 5 years. A small proportion of patients survive longer than 10 years. In this paper we discuss four cases illustrating the nonhomogeneous clinical presentation and evolution of this subset of patients. Surprisingly, these long survivors do not always have deep responses and some require frequent treatments, which include autologous stem cell transplantation and novel drugs. The authors discuss several aspects of these clinical histories, including treatment options, raising hypothesis on their relation with long survivorship which may be important to have in consideration when studying this subject.

Keywords

Clinical characteristics in multiple myeloma, cytogenetics, multiple myeloma long survivors, toxicities.

Introduction

Multiple myeloma (MM) is, generally, an incurable progressive neoplasm accounting for 10% of all hematological malignancies. It was estimated in 2012 that 21,700 new cases and 10,710 deaths from the disease occurred in the United States [1]. In the European Union, there were ~38,900 new cases and 24,300 deaths due to MM in 2012, with only 10% of patients currently surviving longer than 10 years [2, 3]. This small but growing subset of patients is still poorly characterized. The prevalence of this neoplasm, the better knowledge of MM biology, and the availability of new treatment options set the importance of analyzing long survivors among this group of patients.

Novel drugs used in MM include proteasome inhibitors, and immunomodulators and newer molecules are still under clinical development. Compared to the conventional chemotherapeutic agents, proteasome inhibitors and immunomodulators have distinct, more specific mechanisms of action. They are potent effectors, interfering directly with the neoplastic plasma cells and the surrounding microenvironment, leading to high response rates and prolonged overall and progression-free survival [4]. Their combina-

tion with dexamethasone or conventional chemotherapeutic agents results in response rates comparable to those produced by autologous stem cell transplantation (ASCT) [5, 6]. Recently, the continued improvement in overall survival of MM patients treated with novel agents was confirmed regardless of age [7]. However, other clinical and biological characteristics of the disease as well as patient- and drug-dependent factors, such as treatment toxicities, dramatically influence survival.

Well-defined molecular abnormalities are associated with poor outcomes in MM, and gene expression profiles and cytogenetic abnormalities can determine the patients' prognosis [8, 9, 10, 11, 12]. Almost all MM patients harbor genomic abnormalities including structural and numeric chromosomal variations, with variable complexity. This is an indication of genomic instability and intrinsic oncogenic properties and/or failure of protective cellular mechanisms. Myeloma-initiating events such as hyperdiploidy and chromosomal translocations leading to activation of oncogenes, as CCND1, CCND2, c-MAF (V-maf musculoaponeurotic fibrosarcoma oncogene homolog), and MMSET (multiple myeloma SET domain) are important, but not sufficient, determinants of disease

aggressiveness. Secondary events, including activation of oncogenes, such as RAS (RAT sarcoma) and MYC (myelocytomatosis viral oncogene), of NF- κ B and inactivation of tumor suppressor genes such as TP53 and RB (retinoblastoma), are the markers of high-risk disease that characterize patients with a very poor prognosis [13, 14].

Concurrent to biological disease characteristics, clinical variables related to MM (including the ones validated in the International Score System) advanced age and comorbidities also have an important negative impact. An appropriate assessment of organ dysfunction at the beginning of therapy may allow to better define treatment strategies, improving tolerability and optimizing efficacy, especially in the elderly [15, 16, 17].

Toxicities associated to different treatments impact in quality of life. Neurological, hematopoietic, and cardiac side effects are the most common toxicities in patients under prolonged treatment. They are associated to the broad use of alkylating agents, corticosteroids and, more recently, proteasome inhibitors and immunomodulators. Also, survivors of MM are confronted with nonspecific, cancer treatment-related long-term symptoms, most commonly fatigue, sexual dysfunction, arthralgia, and a high risk of second primary malignancies (SPM) [18]. High-dose chemotherapy with autologous stem cell support became widely used since 1990s in fit patients under 65 years of age. Despite employing high doses of melphalan, the risk of myelodysplastic syndromes/acute myeloid leukemia after transplant is estimated to be less than 5%, mostly attributable to pretransplant therapy [19]. Also, no significant risk change was noted after the introduction of autologous stem cell transplant among younger patients (<65 years) and other novel agents [20, 21]. Recent studies have reported an increased risk of second primary cancers following treatments with immunomodulators, possibly reflecting longer survival times. Recent published data showed that this risk does not increase over time.

Patients with MM who are considered long survivors are usually young patients, without high-risk cytogenetic features and international staging score (ISS) 1, low tumor burden (absence of severe anemia, hypercalcaemia, renal failure, or multiple bone lesions), absence of Bence-Jones proteinuria, low-plasma cell percentage in bone marrow, mature and intermediate myeloma. Also, a positive response to first-line treatment and to subsequent treatments were related to long-term survival [19, 20, 21]. Interestingly, it seems that long-term survival in MM is associated with a distinct immunological profile, which includes proliferative cytotoxic T-cell clones and a favorable Treg/Th17 balance [22].

With the aim of examining some factors that influence long-term survivorship, we present and discuss four different clinical cases of long-term survivors with MM,

including both transplanted and nontransplanted patients with a variety of comorbidities and different treatments flows. These four patients diagnosed with MM for more than 10 years (13, 18, 19, and 20 years) were selected from the authors' outpatient practice because they were alive and are representative of the true story and heterogeneity of MM worldwide. The cases are summarized first and followed by a common discussion.

Case 1

A Caucasian 56-year-old man with no relevant past medical history was diagnosed with MM IgG kappa, Durie Salmon stage IIIA, ISS II in July 1996. At diagnosis, he had a performance status (PS) of 1 and presented with a bone marrow plasmocytosis of 65.5%, serum IgG 10,600 mg/dL, anemia (Hb = 10.5 g/dL), and lumbar lytic lesions. At that time no cytogenetic abnormalities were screened by fluorescent in situ hybridization (FISH) and later (in 2011) no FISH abnormalities were detected.

First-line treatment with melphalan and prednisolone (MP) and radiotherapy (D12-L2 – 30 Gy) were started, but suspended after three cycles due to deep venous thrombosis. Partial response was achieved and the patient remained stable until 1997.

In March and May 1997, the patient underwent tandem ASCT without further treatment, achieving a complete response by the International Myeloma Working Group criteria [23]. Maintenance treatment with alpha-interferon was administered for 2 years.

Biochemical disease progression was documented in May 2002 with positive serum immunofixation, but due to the absence of clinical symptoms, treatment was postponed until December 2002, when thalidomide and prednisolone were started due to bone pain and increased serum Ig levels. After 12 cycles, thalidomide dose was reduced to 50 mg/day due to grade 2 peripheral neuropathy. The neurologic toxicity motivated the interruption of the treatment in March 2005, despite the achievement of very good partial response (VGPR).

Retreatment was not necessary until October 2008, when bone pain reappeared and an increased serum Ig level was detected. The patient was started on with lenalidomide (monthly cycles of 25 mg/day for 21 days) and dexamethasone (40 mg/week). Aspirin 100 mg/day was added as thromboprophylaxis. The patient has been kept on the same treatment and completed 20 cycles. An ongoing complete response was documented after the 11th cycle.

Case 2

A Caucasian 58-year-old woman with a medical history of Hepatitis C, epilepsy, intestinal angiodysplasia with

previous bleeding episodes, major depression, and a PS of 0 was diagnosed with IgG kappa MM, Durie Salmon stage IIIA (ISS not available), in June 1994. At diagnosis, she had 13% bone marrow infiltration by plasma cells, serum IgG of 8731 mg/dL, and multiple painful osteolytic lesions. At that time no cytogenetic abnormalities were screened by FISH and in 2009 no FISH abnormalities were detected.

First-line treatment with MP was changed to cyclophosphamide and prednisolone due to no response. This second line of treatment was maintained for four cycles and the patient achieved stable disease. In March 1997, she presented with bone pain, rising serum levels of monoclonal protein and hepatomegaly, which led to the introduction of the third line of treatment with vincristine, melphalan, cyclophosphamide, and prednisone (VMCP) alternating with vincristine, carmustine (BCNU), doxorubicin, and prednisone (VBAP) (VMCP/VBAP). After four cycles, a fracture in D12 with cord compression occurred. After local radiotherapy (30 Gy), she continued treatment with six cycles of infused vincristine, adriamycin, and high-dose methylprednisolone (VAMP), which was complicated by hematologic and infectious toxicity, grades 2 and 3 respectively. Still, symptoms improved and the hepatomegaly receded but by the end of the treatment IgG had stabilized at 7200 mg/dL and 3.5% plasma cells persisted in the bone marrow.

Due to clinical stability and chemotherapy-related toxicities, the patient was kept without therapy for 3 years. In 2001, she restarted VBAP (fifth line) due to biochemical progression and recurrence of pain. Partial response was achieved after 12 cycles. In August 2002, clinical and biochemical progression lead to treatment with thalidomide plus dexamethasone (sixth line) for 14 months, with grade 2 neuropathy. However, a long-lasting partial response was achieved and remained stable for almost 5 years. During that period, New York Heart Association class II–III heart failure was diagnosed and attributed to previous treatment with anthracyclins.

By the end of 2008, back pain increased and serum monoclonal protein rose, and thalidomide and dexamethasone were restarted and kept until March 2010. The persistence of neurological and cardiac toxicity, lead to treatment interruption. Again, a partial response was obtained that lasted for 24 months. In January 2012, a new clinical relapse was treated with cyclophosphamide and prednisolone without success. Treatment with lenalidomide plus dexamethasone was begun and warfarin was used as thromboprophylaxis. The symptoms improved and her hemoglobin values rose. She stopped erythropoietin in January 2013. She is currently in partial response. No major side effects were documented and no delays in chemotherapy were needed.

Case 3

A Caucasian 32-year-old man with no relevant past medical history and a PS of 3 due to bone pain was diagnosed with IgG lambda MM, Durie Salmon stage IIA, ISS I in July 1995. At diagnosis, he presented marrow plasmacytosis of 2.3%, serum IgG of 3238 mg/dL, 14.6 g/dL of hemoglobin, and one osseous plasmocytoma on the left femur that led to a pathological fracture. At that time no cytogenetic abnormalities were screened by FISH and in 2005 and 2012 no FISH abnormalities were detected.

Right after diagnosis, first-line treatment with cyclophosphamide and prednisone for two cycles and local radiotherapy (RT) (40 Gy) were started, followed by vincristine, doxorubicin, and dexamethasone (VAD) for six cycles, without major toxicities. Partial response was achieved and the patient underwent tandem ASCT in 1996 (melphalan 200 mg/m² in conditioning for both) with 2 years maintenance therapy with alpha-interferon. He reached a VGPR and remained without further treatment for 7 years.

In February 2005, bone pain and increasing serum M component and bone marrow plasmacytosis were detected. A third line of chemotherapy with cyclophosphamide plus dexamethasone and additional RT to control painful bone lesions was started. After four cycles without response, a fourth line of treatment was initiated with bortezomib and dexamethasone (VD). After eight cycles he had had no major toxic events and achieved a VGPR. He was proposed for a third ASCT that took place in May 2006 (melphalan 140 mg/m²), keeping a VGPR.

The patient remained clinically stable, with slow biochemical progression after transplantation. In July 2007, a fifth line of treatment with thalidomide and cyclophosphamide was initiated. A partial response was achieved, with grade 2 neurotoxicity, which lead to treatment interruption after eight cycles.

Four months later, progression was documented with bone pain and an increase in bone marrow plasmacytosis. A sixth line of treatment with lenalidomide and dexamethasone was introduced and a partial response was achieved. This treatment continued until November 2010, when the patient was admitted in the emergency room with paraplegia due to dorsal vertebra collapse and spinal cord compression. Emergency decompressive neurosurgery was performed with complete neurological recovery. He then initiated seventh treatment line with bortezomib, cyclophosphamide, and dexamethasone, which was maintained for 23 cycles and suspended in July 2012 due to grade 3 neuropathy and frequent respiratory infections. The best response achieved was stable disease. In January 2011 radiotherapy was again necessary for bone pain control.

Six months later, the patient started his eighth therapeutic line (idarrubicine and dexamethasone, interrupted due to toxicities without response).

He was then started on pomalidomide and low-dose dexamethasone. Repeated infectious and hematological adverse events occurred, and the disease progressed after four cycles. Currently, the patient has stable disease under cyclophosphamide and dexamethasone.

Case 4

A 56 year-old woman patient with no relevant past clinical history, was diagnosed with MM IgG kappa, Durie Salmon stage IIB, ISS stage III in December 2001. At diagnosis, the patient presented bone marrow plasmocytosis of 68.4%, serum IgG of 1500 mg/dL, anemia and renal insufficiency (Hb 9.2 g/dL, serum creatinine 1.6 mg/dL). At that time no cytogenetic abnormalities were detected by FISH, but a del 13q14 was identified in 2002.

Right after diagnosis, treatment with VAMP for four cycles was initiated. The patient developed renal failure and hemodialysis was started. The treatment was altered to cyclophosphamide and prednisolone, and kept for 12 cycles with the achievement of PR without renal function recovery.

In July 2003 disease progression with bone pain and increased serum IgG lead to a third line of treatment with thalidomide and dexamethasone. The patient achieved VGPR by the 18th cycle, with grade 2 neuropathy. In November 2006, thrombosis of the hemodialysis fistula occurred despite the thromboprophylaxis with aspirin.

The patient was kept on the same regimen until October 2008, when disease progression (painful bone lesions) was observed. Radiotherapy, vertebroplasty, and treatment with high-dose dexamethasone (fourth line) were started. The patient completed 12 cycles in September 2009, achieving VGPR.

She was kept on observation until January 2013, when *de novo* lower back and right hip pain started. New bone lesions and a soft tissue mass in the right femur were documented without changes on bone marrow plasmocytosis or biochemical progression. Local radiotherapy improved the symptoms. At last follow-up, the disease is stable without further treatment.

Discussion and Conclusion

The term “long-term survivor” in oncology refers to patients alive for 10 or more years after the diagnosis of cancer. In the case of MM, long-term survival is still unusual and less than 10% of patients fulfill this criteria [4, 7].

Nowadays, with expanded overall survival and a population well aware of health information, myeloma patients frequently discuss survival issues with their physicians and it is important to note that both the overall and disease-free survival of those patients have been significantly prolonged due to newer and more target-specific treatments and adequate supportive care [4, 7, 24].

The cases presented here are good examples of long-term MM control with different sequential treatment strategies. While patient 3 clearly benefited from conventional chemotherapy (mainly melphalan), patients 1 and 2 were particularly responsive to immunomodulation. All enjoyed prolonged treatment-free intervals. Although we did not identify specific biological or genetic characteristics in these cases, they differ from the more commonly observed pattern of progressively shorter remissions after multiple relapses.

Besides treatment options, prolongation of survival is, in some cases (as illustrated in case 1), not simply related to the use of novel drugs but possibly associated to clinical prognostic factors and biological characteristics of the disease. Cytogenetic and molecular characteristics of clonal plasma cells are well-defined as prognostic factors based on the results of several myeloma biology studies and clinical trials [6, 11, 25, 26, 27, 28].

Although each patient had a different profile of response all were long survivors. As such, there seems to be, not one, but several profiles of long survivors in MM.

Case 1 exemplifies a highly chemo- and immunomodulation-sensitive disease, as shown by good responses to all treatment lines for the last 17 years. In this case, the prolongation of survival was evident even before the introduction of new drugs. Notably the patient received only three treatment lines and was never exposed to proteasome inhibitors. This type of tumor allows treatment strategies that may even exclude high-dose melphalan and autologous transplantation, as suggested by the Mayo Clinic treatment approach [29]. This case is also an example of potential advantages for maintenance treatment approaches that may prolong responses and, subsequently, overall survival.

Case 2 is a MM patient diagnosed 19 years ago. She received mostly conventional chemotherapy regimens and achieved mainly partial responses. With the introduction of thalidomide, more prolonged disease control was possible at the cost of neurotoxicity that finally led to treatment discontinuation. Currently this patient is under lenalidomide and dexamethasone and achieved a new partial response with significantly less toxicity. In this case, a proteasome inhibitor was never used. The neurotoxicity associated to the extensive use of thalidomide is now known to preclude or delay treatment with bortezomib, which must be taken in consideration when planning the therapeutic approach to this chronic disease.

Case 3 exemplifies the advantage of high-dose melphalan and ASCT as a pathway to achieve better responses and prolonged survival, even before the introduction of novel drugs. This patient was diagnosed at an early age and underwent three ASCT and several treatment lines with a wide range of anti-MM drugs, including experimental agents (pomalidomide). In this case, FISH studies did not show any abnormality. However, the long clinical course may have allowed an evolution through sequential sensitive clones. More sensitive molecular methodologies such as gene expression studies or DNA sequencing might enlighten relevant genetic features explaining chemosensitivity in similar clinical settings. This case is also an example of the need for a multidisciplinary team to optimize MM patient care, as well as of the importance of maximizing the use of current drugs in order to allow future access to drugs still under development.

Patient 4 illustrates the case of an early acute renal failure complicating a diagnosis of MM in a young woman, who became dependent of dialysis regardless of what was considered standard chemotherapy at that time. However, even in this poor setting, deep and prolonged disease control was possible. The patient received thalidomide, corticosteroids, and local radiotherapy to control pain related to isolated bone lesions. An improvement on renal function was never achieved and neurological, thromboembolic, and metabolic toxicities occurred over time, which precluded the use of proteasome inhibitors. However, a reasonable quality of life is maintained and the disease was controlled with few treatment lines and limited use of novel agents.

In addition to treatment options, long survival of myeloma patients might be related to biological characteristics of tumor cells and/or microenvironment. Disease biology is indeed one of the most important determinants of outcome. Among patients with similar age, comorbidities, and disease stage, survival can vary widely based on genetic markers of aggressiveness [21, 30]. Although scores based on cytogenetic abnormalities are used for prognostic stratification, they not always directly dictate treatments [9]. As such, detailed cytogenetic and molecular studies were not performed in the long-term survivors presented here and cannot be used as an explanation for the observed outcomes.

These observations underline the importance of other variables interfering with overall survival, including comorbidities and fitness. These are typically approached in the clinics by modifying treatment intensity and tailoring therapeutic approaches. In this sense, hematologists tend to avoid ASCT in patients with advanced age, and often reduce the dose and intensity of chemotherapy to minimize toxic side effects and maximize control of the disease. However, a recent study showed that ASCT is

feasible and well-tolerated in selected MM patients aged >65. With the limitations of a retrospective case-match analysis and differences in the treatments, novel agents incorporated into ASCT seem to offer better outcomes in comparison with novel agent-based treatments alone and should be considered a valid option for fit elderly patients [31]. On the other hand, the role of ASCT to treat fit and young patients with MM was recently questioned as several studies questioning the need for such an aggressive approach are ongoing (studies from the European Myeloma Network and Italian group). Results from these studies will help to clarify this question.

Better, patient-centered health care, aiming at specific problems occurring in long survivors may minimize some of the adverse events and increase quality of life. Multidisciplinary teams of health professionals including physicians, psychologists, nutritionists, and physical therapists may contribute to better evaluate the needs of long survivors and design comprehensive survivor programs. Besides therapeutic antimyeloma strategies aiming to control residual disease, these survivor programs may include special attention to patient comorbidities, toxicity management, and physical, psychological, and social rehabilitation. Current approaches to cancer survivorship care should include the integration of health care perspectives with the needs of cancer survivors and the optimization of practices in cancer survivorship care, overcoming barriers for personalized approaches and exploring areas for future research aimed at improving the quality of life [32, 33].

The observed prolongation on MM patients' survival may allow statisticians to apply "cure models" as an alternative to the standard Cox proportional hazards models to data showing prolonged survival trends [34, 35]. These models may allow researchers to investigate what covariates are associated with either short- or long-term effects. The cases presented here are, however, good examples of prolonged survival with reasonable controlled but persistent disease. It is important to incorporate the concept of quality of life in the management of these patients and appreciate that long survivorship, even not leading to cure, is very dependent on treatment strategies.

Currently, and given the prolongation of survival, we may point three major controversies in MM management: early versus late transplant, treatment or observation in "high-risk" smoldering myeloma, and use of maintenance/prolonged therapy. These controversies and the answers hematologists may prefer are associated with the perception of risks and benefits associated to each of the choices. Although it is common thinking that patients should receive upfront treatment with a triple or quadruple combination of drugs, there is no absolute evidence pointing to the need for combined therapies in the begin-

ning of symptomatic disease; sequencing novel agents, saving options for a later relapse, may be an alternative and effective strategy in some cases. New phase III clinical trials are needed to specifically address and clarify these questions. Recently the concept of clonal evolution through tides among the population of myeloma cells showed the presence of several clones of tumor cells at diagnosis, each with a different genetic makeup. The results of that work also show that the dominant clone changes over the course of the disease and is influenced by treatments, with a given clone rising and falling over time (known as clonal tides) [13]. These concepts provide a rational basis for the definition of optimal sequential treatment strategies for specific groups of MM patients, maximizing the survival benefit through the appropriate choice of drugs at different time-points. While the clinical availability of such tools is limited to some centers, survival of MM patients depends not only on the availability of multiple drug options but also on the personalized decisions and multidisciplinary teams providing adequate care during different stages of the disease, including (and leading to) long survivorship.

Conflict of Interest

None declared.

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