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REVIEW ARTICLE

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A historical perspective on milestones in multiple myeloma research

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Abstract

The first well-documented case of multiple myeloma was reported in 1844 by Samuel Solly. In this article, the author presents a historical review of the disease. In particular, the review is focused on the main steps, including the definition of Bence Jones proteinuria, the characterization of tumoral plasma cells and serum globulins, and the fundamental contribution of Jan Waldenstrom. Finally, treatment of multiple myeloma, as well as the development of new agents, is discussed.

KEYWORDS

hematology, history of medicine, multiple myeloma, tumor growth

1 | THE FIRST CASE AND THE FIRST DEFINITION OF THE DISEASE

The first well-documented case of multiple myeloma, just based on the clinical presentation, was described by Solly[1] in 1844. The patient, Sarah Newbury, was a 39-year-old housewife who had developed severe back pain. She died 4 years after the onset of symptoms, and the postmortem examination revealed that a red substance had replaced the cancellous portion of the sternum as well as both femurs. Autopsy revealed fractures of the right radius and ulna, left tibia and fibula, and both femurs. The term multiple myeloma was introduced by von Rustizky in 1873[2] while he was working in the institute of professor von Recklinghausen. At the autopsy of a patient, he found eight separate tumors of the bone marrow, soft in consistency and reddish in color designated as "multiple myeloma".[2] In 1889, Kahler[3] (Figure 1) described a case of a 46-year-old physician with multiple myeloma and described the skeletal pain, albuminuria, pallor, anemia, a precipitable urinary protein, and the findings on necroscopy. In 1928, Geschickter and Copeland reviewed the 412 cases reported in the literature since 1848.

2 | BENCE JONES PROTEINURIA

In 1845, in the St. George's Hospital in London, William MacIntyre, Henry Bence Jones (Figure 2), and John Dalrymple examined a patient of MacIntyre admitted to the hospital with vague but uninterrupted pain in the chest, back, and pelvis. MacIntyre called Henry Bence Jones and asked him to test the patient's urine. Bence Jones found a substance in the urine that was precipitated by addition of nitric acid. He noted that the precipitate was soluble in boiling water but reprecipitated after the urine was cooled. He stated that the patient had "albumosuria." Soon after the urine was tested, the patient died. Jones concluded that the protein was an "oxide of albumen" and from the ultimate analysis was the "hydrated deutoxide of albumen".[4,5]

The patient died on January 2, 1846. Dalrymple, the pathologist, performed an autopsy and observed that the sternum and cervical, thoracic, and lumbar vertebrae were soft, fragile, and easily breakable, and could be cut with a knife. Moreover, multiple hemorrhagic cavities in bones throughout the body were recognizable. In 1846, Dalrymple summarized the pertinent postmortem findings and suggested that the disease began in the cancellous bone and extended through the periosteum.[6]

In 1847, Bence Jones reported his premortem findings in a short note in the Lancet.[4] A year later, he published a definitive paper on his laboratory findings with a detailed description of the technique he had used to analyze the urine.[5] In 1850, MacIntyre summarized the case from the clinician's point of view.[7]

The cause of death was given as "atrophy from albuminuria".[8] At that time, albuminuria was the term used nonspecifically to mean proteinuria, while the term "Bence Jones protein" was first used by Fleischer in 1880.[9] In 1898, Weber postulated that the bone marrow is the site of production of the Bence Jones protein. In 1917 and 1921, respectively, Jacobson and Walters recognized Bence Jones proteins

FIGURE 1 A port trait of Otto Kahler (from Universitat Wien website)

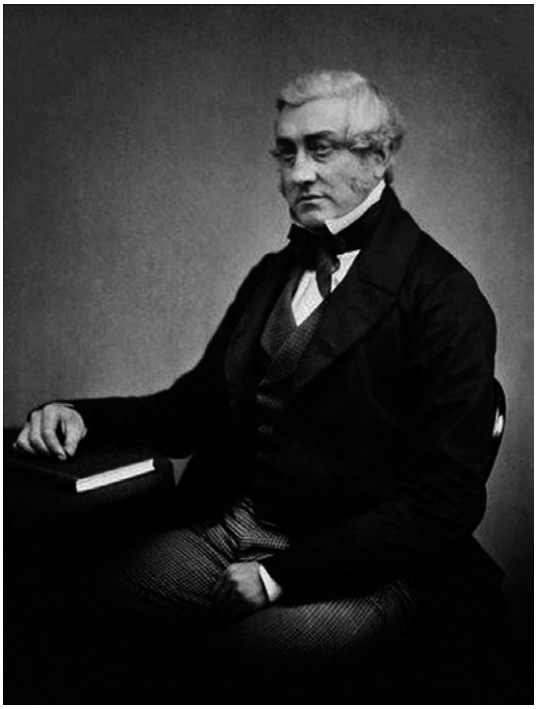

FIGURE 2 A port trait of Henry Bence Jones (from Wikipedia)

in the bloodstream and considered that it was probably derived from blood proteins through the action of abnormal cells in the bone marrow. In 1922, Bayne-Jones and Wilson[10] described two groups of Bence Jones protein by immunizing rabbits with Bence Jones proteins from patients.

In 1939, Longsworth and coworkers[11] applied electrophoresis to the study of multiple myeloma and demonstrated the tall narrow-based "church spire" peak (Figure 3). Electrophoresis was not readily available until the early 1950s, when filter paper was introduced as a supporting medium. In 1957, cellulose acetate supplanted filter paper[12] and then agarose gel. In 1953, Grabar and Williams[13] described immunoelectrophoresis, which facilitates the diagnosis of multiple myeloma. Immunofixation or direct immunoelectrophoresis was described by Wilson in 1964.[14] Monoclonal immunoglobulins are detected by serum and urine protein electrophoresis, followed by immunofixation. Immunoelectrophoresis and immunofixation or direct immunoelectrophoresis make it possible to detect small monoclonal light chains not recognizable on electrophoresis. Protein electrophoresis is based on the principle that proteins migrate at different rates according to their unique electrical charge. Immunoglobulins migrate to gamma region during electrophoresis, and the presence of monoclonal immunoglobulin produced a distinct "M-spike" in the gamma region not seen in normal individuals.

In 1956, Korngold[15] from Memorial Hospital and Rose Lipari, his technician, identified different classes of Bence Jones proteins. They also demonstrated that antisera to Bence Jones protein also reacted with the myeloma protein in the blood. As a tribute to Korngold and Lipari, the two classes of Bence Jones proteins have been designated kappa and lambda. Two years later, Harold Porter from England split the antibody into two major parts, the heavy chains and the light chains.

In 1962, Edelman, Nobel Prize in Medicine or Physiology or Medicine in 1972 along with Porter for their discoveries concerning the chemical structure of antibodies (Figure 4), and Gally looked at the light chains of a patient who had a multiple myeloma with a typical M-spike in the serum. This M-spike for this particular patient was broken down into the heavy and light chains, and it was demonstrated by Edelman that the light chains in the immunoglobulin molecule in the spike of the monoclonal protein that this light chain was absolutely identical to the Bence Jones protein that the patient

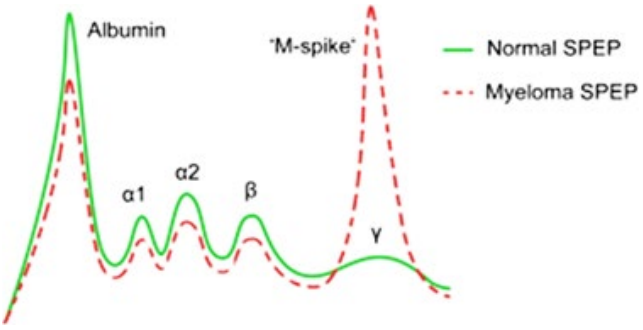

FIGURE 3 Myeloma serum protein electrophoresis. In a serum protein electrophoresis test, a healthy patient exhibit peaks in the albumin, α1, α2, β region, with a "smooth shoulder" in the γ region. A patient with multiple myeloma in contrast exhibits a distinct "M-spike" in the γ region, indicative of excess Ig. SPEP, pattern serum protein electrophoresis

FIGURE 4 A port trait of Gerald Edelman (from Wikipedia)

FIGURE 5 A port trait of Arne Wilhelm Kaurin Tiselius (from Wikipedia)

excreted. As Edelman wrote: "Given my hypothesis about myelomas, the thought arose that perhaps Bence Jones protein was one of the chains of the myeloma protein that spilled into the urine because of its relatively low molecular weight (about 22,000)".[16] Edelman decided to study these proteins, and after he compared reduced myeloma proteins from a number of different patients, he demonstrated that each protein when reduced and alkylated and subjected to starch gel electrophoresis had a unique migration pattern.[17] Bence Jones proteins were simple excreted light chains. Edelman heated a sample of light chain obtained from normal human serum gamma globulins and demonstrated that they had the behavior of Bence Jones proteins becoming insoluble and then resolubilizing with continued heating.[18]

In 1967, Putman et al demonstrated that different Bence Jones proteins were different in their peptide sequence. As Edelman wrote: "The key experiment was to use the recently discovered starch gel electrophoresis to take a whole bunch of patients' urine samples, separate their Bence Jones proteins, and simultaneously separate and compare their serum proteins. When we ran the electrophoresis we demonstrated that the light chains were the Bence Jones proteins and they were pure and no two had the same mobility pattern".[16]

3 | TUMORAL PLASMA CELLS

The mature effectors of the B-cell lineage are terminally differentiated, non-dividing, antibody-secreting plasma cells. Multiple myeloma results from malignant transformation of plasma cells or their precursors.

In 1948, Bayrd[19] showed for the first time that patients with very immature plasma cell morphology had a shortened survival. However, the assessment of these cells allows the identification of only a small proportion of patients. More recently, plasma cell morphology has been investigated using a progressive evaluation of consecutive criteria: nucleolus, chromatin, and nuclear-cellular ratio.[20] The combination of these three-four cellular subtypes identifies 93% of the plasma cells, and these subtypes are related to the outcome. The malignant plasma cells are localized to the bone marrow in close association with stromal cells, but are rarely found in other locations. They are long-lived plasma cells and are still able to proliferate, although at a very low rate. The rearranged immunoglobulin genes of malignant plasma cells are extensively somatically hypermutated in a manner compatible with antigen selection, but in contrast to their normal counterparts, the multiple myeloma cells lack terminal differentiation and they produce significantly lower amounts of immunoglobulins.

In an individual with multiple myeloma, a normal and functional polyclonal Ig population is replaced by massive amounts of monoclonal Ig produced by myeloma cells.[21] The accumulation of myeloma cells inside the bone marrow is responsible for symptoms of multiple myeloma and systemic complications. Patients usually experience anemia and immune deficiencies due to an overall reduced production of blood cells, as hematopoietic tissues are replaced with myeloma cells.[22]

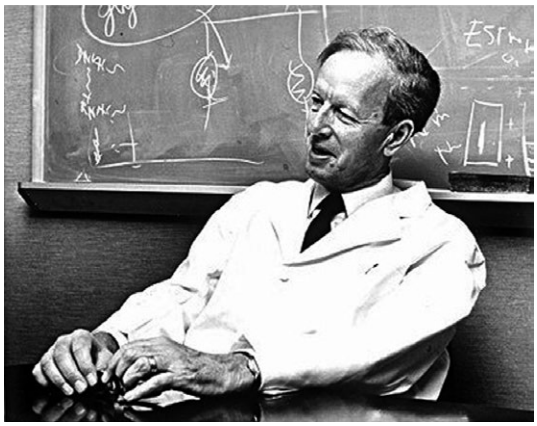

FIGURE 6 A port trait of Jan Waldenstrom (from ref. [67]

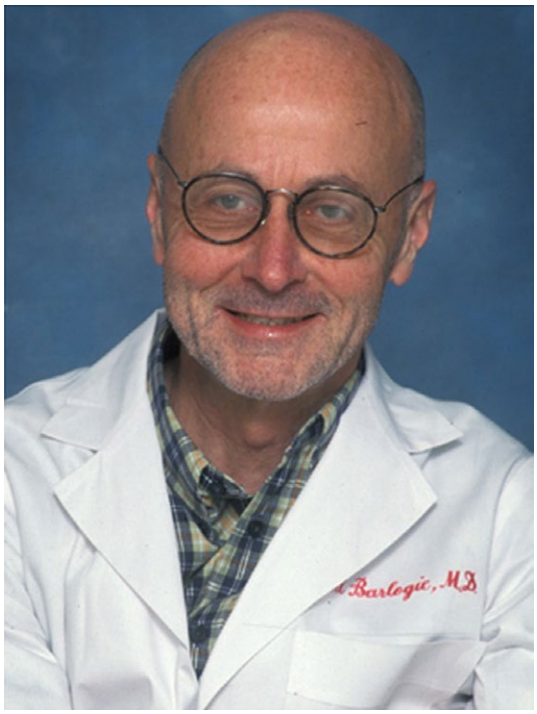

FIGURE 7 A port trait of Bart Barlogie (from UAMS.edu website)

4 | SERUM GLOBULINS

In 1937, Tiselius,[23] Nobel Prize in Chemistry in 1948 for his research on electrophoresis and adsorption analysis (Figure 5), using electrophoresis separated serum globulins into three components, which he designated α, β, and γ. Healthy individuals produce five different isotypes of Ig heavy chains (IgH), as well as two different types of light chains (IgL); a myeloma patient may produce monoclonal immunoglobulins (Ig) within any of these isotypes (except IgE isotype). IFE is more sensitive than serum and urine protein electrophoresis (SPEP and UPEP) and may detect patients with low levels of monoclonal Ig. Monoclonal Ig with IgG isotype occurs most frequently in myeloma patients (52%), followed by IgA (21%), IgD (2%), IgM (0.5%). A certain population of myeloma patients do not produce any IgH, but instead produce only IgL (16% of patients). In patients producing IgL only, serum-free light chain assay has been introduced recently for IgL detection.

TABLE 1 Patient overall survival (OS) and progression-free survival (PFS) in multiple myeloma treatment

Treatment	OS	PFS
MTP	50% at 52 mo	50% at 28 mo
TAD	73 mo	34 mo
VAD	60 mo	22 mo
CVAD	63 mo	25 mo
PAD	60 mo	35 mo
TD	84% at 36 mo	56% at 36 mo
VRD	97% at 18 mo	75% at 18 mo
VTD	86% at 36 mo	68% at 36 mo

MTP, melphalan-prednisone-thalidomide; TAD, thalidomide-doxorubicin-dexamethasone; VAD, vincristine-doxorubicin-dexamethasone; CVAD, cyclophosphamide-bortezomib-doxorubicin-dexamethasone;PAD,bortezomib-doxorubicin-dexamethasone; TD, thalidomide-dexamethasone; VRD, bortezomib-lenalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.

5 | WALDENSTROM'S CONTRIBUTION

In 1944, Waldenstrom (Figure 6) described two patients with oronasal bleeding, lymphadenopathy, normochromic anemia, increased erythrocyte sedimentation rate (ESR), thrombocytopenia, hypoalbuminemia, low serum fibrinogen, and increased numbers of lymphoid cells in the bone marrow. The oronasal bleeding could have been related to hyperviscosity, and anemia could be related to increased plasma volume and reduced erythropoiesis. Waldenstrom introduced the concept of monoclonal vs polyclonal gammopathies in the Harvey Lecture series in 1961.[24] Patients with monoclonal proteins have multiple myeloma or macroglobulinemia, while those with polyclonal hypergammaglobulinemia have an inflammatory or infectious process. These patients were considered to have "essential hypergammaglobulinemia" or "a benign monoclonal protein," substituted with the term monoclonal gammopathy of undetermined significance (MGUS).[25]

Waldenstrom described patients with a narrow band of hypergammaglobulinemia as having a monoclonal protein and further correctly regarded the broad band of hypergammaglobulinemia as a polyclonal increase in proteins. Patients with a monoclonal gammopathy already have or may develop a neoplastic process, whereas patients with a polyclonal gammopathy have an inflammatory or reactive cause of their hypergammaglobulinemia.[26]

6 | TREATMENT

Early remedies included rhubarb, leeches, and quinine.[27] Urethane was the first purposeful drug for treating multiple myeloma and was

first used by Alwall in 1947.[28] Toxic effects included severe anorexia, nausea, vomiting, cytopenias, and hepatic damage. It was later found to be highly carcinogenic and proved to be largely ineffective in controlled clinical trials.[29] In fact, the results of this randomized controlled trial of urethane vs placebo in 83 patients with symptomatic multiple myeloma demonstrated that the median overall survival was higher in the placebo group. Many other anticancer drugs were tested against myeloma mouse models and were ineffective at killing myeloma cells.[30] The median overall survival (OS) for myeloma patients at this time was approximately 6 months.[30]

Introduction of chemotherapy agent melphalan in 1962 was the first treatment breakthrough. It was the first drug to show consistent response in myeloma patients. For patients who responded, there was significant tumor regression and reduction in symptoms such as anemia and bone destruction.[31] Successful treatment of multiple myeloma using melphalan and prednisone began on the late 1960s and achieved a median overall survival of 3-4 years. Melphalan or Alkeran was an alkylating agent discovered in 1958 by Blokhin from Moscow at the height of the cold war. It took a bit of time for the drug to make its way first to England where Galton did the first clinical studies in western Europe, and then in 1962, it was studied at MD Anderson by a young faculty member named Danny Bergsagel.[32] The most common side effect of melphalan is myelosuppression, especially thrombocytopenia, but it is otherwise well-tolerated.

In the late 1960s, prednisone was added to melphalan. The combination of oral melphalan and prednisone resulted in additional survival of 6 months when compared to melphalan as single treatment.[33,34] Patients with long-term prednisone therapy had marked thinning of the bone, and many of them developed compression fractures. This is exactly the problem in multiple myeloma, but we found that prednisone enhanced the activity of melphalan, and it became accepted as the treatment.

In 1972, Harley from West Virginia University was the first to combine various alkylating agents, melphalan along with BCNU and cyclophosphamide as well as prednisone. Then, for the next several decades, various combinations of alkylating agents were used.

Changes in treatment standards began when high-dose therapy in multiple myeloma was reported by Tim McElwain from London, The Royal Marsden Hospital, and Powles in 1983.[35] They demonstrated that a single infusion of high-dose melphalan could induce complete remission in patients with high-risk diseases, and this dose-response effect of melphalan was later confirmed in a larger study.[31] To overcome the prolonged myelosuppression induced by high-dose melphalan, systematic autologous stem cell support, which was initially explored in a relapse setting, but was introduced in an upfront setting, was proposed by Barlogie et al[36,37]

In the 1990s, peripheral blood stem cell transplantation (PBSCT) was introduced and was shown to be superior to bone marrow transplantation in terms of hematopoietic recovery, which suggests that peripheral blood is a recommended source of autologous stem cell transplantation (ASCT) in multiple myeloma. With a single high-dose therapy followed by ASCT, 20%-50% patients achieved complete remission; however, almost all patients eventually relapsed.[38]

In 1999, the Arkansas group first reported the concept of double intensification therapy for newly diagnosed multiple myeloma, and prospective randomized trials comparing double vs single high-dose therapy (HDT) have subsequently been investigated.

Significant therapeutic benefits have been achieved with thalidomide, lenalidomide, and bortezomib when combined with conventional therapies. Thalidomide had been introduced in the mid-1950s for nausea and vomiting of pregnancy as well as for the treatment of anxiety. Unfortunately, it was recognized in 1961 or 1962 that this produced congenital anomalies in a number of babies born. The major anomaly was one in which the arms and legs did not develop, a medical condition that is called phocomelia.

Based on the increasing interest for the use of thalidomide as an anti-angiogenic agent, Barlogie (Figure 7) and colleagues at the University of Arkansas initiated a compassionate-use trial of "anti-angiogenic therapy." A woman, Mrs. Wolmer, whose husband's myeloma was then not responsive to any treatment, pressured an oncologist at University of Arkansas, Dr. Barlogie, to try thalidomide due to its anti-angiogenesis properties. Sadly, thalidomide did not work for Mr. Wolmer, but a second patient treated with thalidomide went into complete remission.[39] Barlogie conducted a trial including 84 patients and had 32% of patients respond, making it the first new drug with single-agent activity for myeloma in more than 3 decades.[40]

Three or 4 years later, bortezomib (Velcade) was introduced. It was developed by Julian Adams and was studied by Millennium after basic laboratory studies by Hideshima from Anderson's laboratory, and the clinical trial showed this agent, a proteasome inhibitor, had very definite antimyeloma activity. Bortezomib became available shortly after its efficacy in patients with relapsed refractory multiple myeloma (RRMM) was demonstrated in 2003 and 2004 in two phase II trials (SUMMIT and CREST).[41-43] These studies were followed by a phase III trial comparing bortezomib to high-dose dexamethasone (the APEX trial).[44,45] The studies demonstrated that bortezomib was effective as single agent in patients with RRMM, showing a response rate (partial response (PR) and CR) of 27%-43%. Similar response rates were seen when using single-agent bortezomib as frontline treatment.[46,47]

Then, a new drug, lenalidomide (Revlimid) was introduced. This was a second-generation drug following thalidomide, and this drug could be taken orally, produced only modest side effects, and was an important addition to the treatment for multiple myeloma. Lenalidomide was approved in the United States in 2006 for the treatment of RRMM.[48] When it was combined with dexamethasone, 90% of newly diagnosed patients responded[49] and the combination showed superior response in RRMM compared to dexamethasone alone.[50]The most frequent side effects are neutropenia, thrombocytopenia, and venous thrombosis.[50] Lenalidomide is partly eliminated in urine, and it is therefore necessary to adjust the dose depending on renal function. These three drugs constituted the first novel agents, and this resulted in more benefit for multiple myeloma in the past decade than had been seen in the previous four decades.

It is worthwhile to also mention carfilzomib, a second-generation proteasome inhibitor that binds selectively with the chymotrypsin-like

site of the proteolytic core and is currently examined in different doses and regimens in RRMM as in newly diagnosed MM.[51]

Patients with multiple myeloma who are treated with lenalidomide or thalidomide are at significantly increased risk for thrombotic events, and many physicians incorporate anticoagulation strategies in their management. A study by Palumbo et al determined that aspirin and low-dose warfarin had similar efficacy in reducing serious thromboembolic events, acute cardiovascular events, and sudden deaths in patients with myeloma receiving thalidomide-based regimens compared with low molecular weight heparin, except in elderly patients.[52]

A study by the Southwest Oncology Group compared lenalidomide plus dexamethasone to placebo plus dexamethasone in patients with newly diagnosed myeloma.[53] The study determined that lenalidomide plus dexamethasone had superior 1-year progression-free survival (PFS), overall response rate, and very good partial response rate, suggesting that it is safe and effective as initial therapy for patients with newly diagnosed myeloma.

In February 2015, the FDA approved an expanded indication for multiple myeloma to included newly diagnosed patients. The original indication was for patients who had received at least 1 prior therapy. A phase III randomized, open-label trial of 119 patients with high-risk smoldering multiple myeloma found that early treatment with lenalidomide plus dexamethasone, followed by maintenance therapy with lenalidomide, delayed progression to symptomatic disease and increased overall survival.[54]

Pomalidomide is a newer analogue of thalidomide. Studies have demonstrated the effectiveness of pomalidomide in RRMM patients both as a single agent[55,56] and in combination with low-dose dexamethasone, even in patients refractory to other immunomodulatory drugs (IMiDs) and/or bortezomib.[57-60] A phase III study compared pomalidomide plus low-dose dexamethasone to high-dose dexamethasone and found a longer PFS and a better response rate in the pomalidomide group.[61] The pharmacokinetics of pomalidomide does not seem to be affected by renal impairment, suggesting that it can be administered in full approved dose in patients with kidney failure.

Adjunctive therapy for multiple myeloma includes radiation therapy to target areas of pain, impending pathologic fracture, or existing pathologic fracture. Bisphosphonate therapy serves as prophylaxis (ie, primary, secondary) against skeletal events (eg, hypercalcemia, spinal cord compression, pathologic fracture, need for surgery, need for radiation). Evidence suggests that it may be effective in treating bone pain and in decreasing the likelihood of lesion recurrence[62-64]

New therapies such as heat-shock protein (HSP) 90 inhibitors, Akt inhibitors, histone deacetylase (HDAC) inhibitors, BCL2 inhibitors, pro-apoptotic peptides, and other proteasome inhibitors are in preclinical studies to provide the framework for phase I and II clinical trials. These new agents are tested singly or more commonly, in combination with other multiple myeloma therapies.

Finally, as treatment options in multiple myeloma continue to emerge, one of the most promising class of agents are immunotherapeutic approaches, including monoclonal antibodies, adoptive T-cell therapy, vaccines, and combination therapy.[65] Intravenous daratumumab is the first-in-class human monoclonal antibody against CD38 available for use in patients with RRMM.[66]

Despite therapeutic advances, disease relapse is inevitable and multiple myeloma remains substantially incurable. The arsenal against multiple myeloma is expanding. However, all anticancer drugs including novel therapies have debilitating side effects. In addition, most antimyeloma drugs only benefit a minority of patients. Ability to identify subgroups of patients who will derive the most benefit from a drug with manageable drug-related toxicity is an important step toward improved response rates, safety, and ultimately survival (Table 1).

CONFLICT OF INTEREST

There is no conflict of interest.

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