Robert Kyle, MD  
Laboratory Medicine and Pathology  
Mayo Clinic  
Rochester, Minnesota

Historical Overview of Multiple Myeloma Therapy

I am Robert Kyle from the Mayo Clinic. I have had a longtime interest in multiple myeloma including the history of the disease. The first recorded case was that of Sarah Newbury that was reported over a 170 years ago. This woman presented with bone pain which progressed, and on one occasion, her husband carried her from the fireplace to her bed, and she fractured two of her femurs. She continued to deteriorate and was finally hospitalized at St. Thomas Hospital in London and was treated with orange peel and infusion of rhubarb as well as narcotics. Unfortunately, she died just a few days later, and at autopsy it was found that she had a bone marrow that was very, very red and resembled that of Thomas Alexander McBean. Mr. McBean’s story is better known in the history of multiple myeloma. He is the patient from whom we recognized Bence-Jones proteinuria. In any event, Mr. McBean was a respectable tradesman and became rather tired and rather weak and decided to go to the countryside to regain his health. In so doing, he was walking about one day and stumbled and was seized with a severe pain in his chest. He had to lie on the ground and could scarcely take a breath, and as a matter of fact, that is typical of multiple myeloma pain. The pain is relieved if you do not move. In any event, Mr. McBean, after a bit of time, was able to make his way to the local inn, and there he was treated with a plaster that immobilized him and this, as you might expect, was beneficial for a short period of time, but his pain recurred and then his physician thought and decided to remove a pound of his blood. The major side effect, as you can imagine, would be weakness, but he did not complain of that because his pain disappeared. Then this patient was treated with the application of leeches and this, I think, is the first maintenance therapy for multiple myeloma. Mr. McBean returned to London and had a very good fall and winter, but the next spring his disease recurred and he again had severe pain. He was treated with cupping and moxibustion to no avail and then was treated with steel and quinine, and at that time, quinine was a relatively new agent and had been used for many, many different medical conditions, any type of fever, fatigue, and the like. Steel was also considered to be a very, very important agent, again, to treat everything. With Mr. McBean, his pain disappeared, and that summer he went to the seashore and stated that he was able to walk about as well as any of his companions. That fall, he returned to London, but his pain recurred, and despite many different therapies, he died on January 1, 1846. An autopsy was done and showed that he had very thin bones with many holes in them, multiple fractures, and microscopic examination of his bone marrow revealed large cells. The nucleus was to the side, which is typical of multiple myeloma, and the woodcuts demonstrate these features, and I am quite certain that this does represent multiple myeloma. A sample of his urine had been sent to Henry Bence-Jones who was a young chemical pathologist.
and physician in London. Dr. Jones studied the urine exhaustively and confirmed the fact that it precipitated when heated to 40 to 60 degrees and then this precipitate disappeared upon boiling, and then the specimen, when cooling, the precipitate reappeared. This has subsequently been called Bence-Jones protein. Dr. Jones actually thought this was a deuteride oxide of albumin, which obviously is very incorrect, but he did make the observation that every patient who had mollities ossium, which is softening and breaking of the bone, should be examined for this particular protein.

Then, not much happened for several decades and in the late 90s, in fact I think it was 1898, the statement was made that x-ray examination of the patient was helpful. This would only the three years after Roentgen discovered the x-rays. Then, in 1916 or so, Jacobson reported that Bence-Jones protein could be found in the blood. It is interesting that in the early 1920s, a scientist from Johns Hopkins named Stanhope Bayne-Jones studied Bence-Jones proteins and injected guinea pigs with a variety of these particular proteins. He came to the conclusion that there were two types of Bence-Jones protein, possibly three types. This of course fell upon deaf ears because no one appreciated the observation of Stanhope Bayne-Jones.

In the mid 1950s, Dr. Korngold from Memorial Hospital and his technician, Rose Lipari, studied antibodies raised in rabbits to various Bence-Jones proteins and concluded that there were two types of Bence-Jones protein, type I or II. Two or three years later, Harold Porter from England split the monoclonal antibody into two major parts, the heavy chains and the light chains. Then, two or three years later, Jerry Edelman 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 excreted. This to me was a very impressive finding. It took 115 years from the time of Henry Bence-Jones to discover that the unique protein consisted of the light chains of the myeloma immunoglobulin intact molecule. I might add in passing that it was not until 1928 that elevated levels of globulin were found in the blood of patients with multiple myeloma. These spikes of protein consist of the M-protein, the monoclonal protein, and Bence-Jones proteinuria. It was actually not until 1961 that the concept of monoclonal and polyclonal gammopathies was made by Jan Waldenstrom. This is an extremely important point, one that everyone accepts as the gospel today because a patient with a monoclonal gammopathy either has multiple myeloma, Waldenström’s macroglobulinemia, or AL amyloidosis, and more commonly has a monoclonal gammopathy of undetermined significance which can develop into multiple myeloma. In fact, in passing, I would make the point that virtually all patients with multiple myeloma have a preceding monoclonal gammopathy of undetermined significance, MGUS.

Going on, I want to say a few words about the history of the treatment of multiple myeloma. Prior to 1947, treatment did not exist for multiple myeloma except for
radiation therapy to areas of localized pain. There was no chemotherapy. In that year, Nils Alwall from Sweden described two patients who were given a drug called urethane. This drug produced a reduction in the monoclonal protein or I should say the protein because the monoclonality was not recognized at that time. In addition to the reduction of the protein, the number of plasma cells in the bone marrow decreased. Then, the next major development was the recognition of melphalan or Alkeran, an alkylating agent discovered in 1958 by Professor 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 Dr. 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. Dr. Bergsagel had joined the faculty at MD Anderson a few years before after training in coagulation at the University of Oxford or Oxford University in England, and there, he had studied with Biggs and McFarlane who were very well-known coagulationists. When Dr. Bergsagel, a Canadian by birth, looked for a position, he found one at MD Anderson, and when the head of the medical department there received this drug from England, he asked Dr. Bergsagel to look at it. Dr. Bergsagel said, “Just a minute, I don’t know anything about multiple myeloma, and furthermore, I am not interested in the disease. I am a clotter. I am interested just in the coagulation of blood.” At that time, department chairs had more power than they did today, and the young faculty member did conduct a study utilizing this new drug melphalan, and reported that lo and behold that 8 of the 24 patients responded to this drug, and others confirmed this finding, and this remained the mainstay of the treatment of multiple myeloma for the next 40 years.

During that period of time, very little progress was made. In the late 1960s, we added prednisone to melphalan, and it took us a period of time to accept that sort of thing because prednisone was known to reduce the integrity of bones. In fact, 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, Dr. Jack 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, yours was better than mine, mine was better than the next fellow’s, and we simply presented data and argued back and forth, and unfortunately, I must confess that after almost four decades of this, a very large meta-analysis was done utilizing more than 5,000 patients who had been randomized to receive melphalan and prednisone alone or various combinations of alkylating agents, and there was a perhaps 10% improvement in response with the combination of alkylating agents, but unfortunately, no difference in overall survival.

In the early 1980s, Dr. Tim McElwain from London, The Royal Marsden Hospital, did an autologous stem cell transplant on a patient with plasma cell leukemia. The patient obtained some benefit, and then Dr. McElwain went on with Ray Powles to report seven or eight patients with multiple myeloma who appeared to benefit from an autologous
stem cell transplant. It was very toxic, and not many people were interested in doing it. In the late 1980s, Dr. Barlogie who was at MD Anderson at that time became interested in autologous transplantation and developed techniques in using transplant, and it subsequently became a very important part of the armamentarium for the treatment of multiple myeloma.

Then, in the late 1990s, a patient was seen by Dr. Barlogie at the University of Arkansas who had very refractory disease. This was a young man that I had seen in consultation seven or eight years before and had started him on an alkylating agent regimen. He was age 35 and a very successful cardiologist from New York City. After seven or eight years of alkylating agents and autologous stem cell transplantation, he was “pretty much at the end of the road” as far as medical therapy was concerned. His wife, however, asked Dr. Barlogie if he could do something else for her husband, he was still young, and there must be something else that could be done. She had read about an agent that was being developed by Dr. Judah Folkman at Harvard University. It was an antiangiogenesis drug, and she called Dr. Folkman and said, “Could we have your drug for the treatment of my husband?” and Dr. Folkman said, “Well, it is in the process of development, it will take years actually before it is on the market, but there is a drug that the National Cancer Institute has, a drug called thalidomide which is a very potent antiangiogenesis agent. Why don’t you use that drug?” And then Dr. Folkman told me at a later time that he then called Dr. Barlogie at the insistence of the patient’s wife and advised him to obtain the drug on compassionate usage from the NCI. Dr. Barlogie did so, I think, with some trepidation. This was the drug thalidomide that 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. Fortunately, the drug had not been approved in the US because Dr. Flora Oldham Kelsey Geiling of the FDA wanted more toxicity data before approving the drug. Fortunately, by the time that data became available, it was evident that this drug produced the phocomelia, and consequently, it was not approved in the US.

Now, shifting to the time of the patient's husband who had totally relapsed-refractory disease, Dr. Barlogie did obtain the agent and treated the patient, and unfortunately the patient did not respond and died. However, Dr. Barlogie had another patient who had relapsed-refractory disease and treated this patient with thalidomide, and this patient had a remarkable response. He and Dr. Singhal went on to treat over 80 patients and reported that 30% of these patients with relapsed-refractory disease responded to this drug, and this was the beginning of the novel agents. Three or four years later, bortezomib, or Velcade, was introduced. It was developed by Dr. Julian Adams and was studied by Millennium after basic laboratory studies by Dr. Hideshima from Dr. Anderson’s laboratory, and the clinical trial showed this agent, a proteasome inhibitor, had very definite anti-myeloma activity. Then, two or three years later, a new drug, lenalidomide, or Revlimid, was introduced. This was a second 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. 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. In my opinion, it was the first major advance following the introduction of melphalan in the late 1950s.

Now, in the past year, two new drugs have been approved in this country for patients with multiple myeloma who have relapsed-refractory disease and who have received at least two prior regimens and have either not responded or become resistant to them. These two drugs are carfilzomib and the other is pomalidomide, a third-generation immunomodulatory drug following thalidomide, lenalidomide, and now the new agent pomalidomide. We are indeed in a golden age as far as multiple myeloma is concerned. Unfortunately, multiple myeloma is still an incurable disease despite the fact that we can do so much more for it now than a decade ago. We need to continue our efforts for the future. We obviously need new drugs, new agents that are effective for this disease. We need to continue basic research. We still do not know the cause of multiple myeloma. We do know that multiple myeloma does arise from monoclonal gammopathy of undetermined significance, but what triggers the progression of that small monoclonal protein to a malignant disease is totally unknown. We need to continue with first, basic research. We still cannot cure the disease nor can we convert the patient with multiple myeloma with surety to a monoclonal gammopathy of indeterminate significance, an MGUS. If we were able to do that, that would be the equivalent of cure, and with that, I leave you with those thoughts, and I hope that this is of some interest to you.

Thank you very much for your attention.