Plasma cell leukemia

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In this issue of *Haematologica*, Drake *et al.* report on a very large number of patients with plasma cell leukemia abstracted from the European Group for Blood and Marrow Transplantation.[1] Having analyzed data from 272 patients who underwent autologous stem cell transplantation, they report a median overall survival of 25.7 months and a progression-free survival of 14.3 months. Surprisingly, the achievement of a complete response following transplantation did not provide a survival benefit. Patients with plasma cell leukemia had higher serum β_2 microglobulin levels and more advanced stage disease. Treatment-related mortality was higher than in a contemporaneous cohort of myeloma patients.

These results should not be generalized to a broader population of patients with plasma cell leukemia. A limitation of all registry studies is that the population does not represent an intent-to-treat cohort. Patients had to survive to receive their autograft and, with a median time to transplant of 6 months, nearly a quarter of patients presenting with plasma cell leukemia would have been expected to have died of their disease. Moreover, none of the patients was transplanted in relapse and none had primary refractory disease, suggesting both chemotherapy responsiveness and a minimal durability of response in order to be acceptable for stem cell transplantation were applied as selection criteria. The results reported here are expected to be substantially better than one might expect when seeing a patient presenting with plasma cell leukemia in clinical practice.

Patients with plasma cell leukemia represent a unique subset of patients with multiple myeloma. The diagnosis requires that: (i) for a blood leukocyte count exceeding 10×10^9/L, at least 2×10^9/L are circulating plasma cells, or (ii) for a peripheral blood leukocyte count below 10×10^9/L, at least 20% of the circulating cells must be plasma cells. The leukemia is classified as primary when this is the initial presenting manifestation of multiple myeloma, or secondary when it is seen in the context of refractory or relapsing disease.[2] From 1960 through 2008, of 6974 new patients with multiple myeloma seen at the Mayo Clinic, 90 fulfilled the criteria for having plasma cell leukemia (1.3%). In an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, there were 49,106 patients with multiple myeloma; 291 had plasma cell leukemia (0.5%).[3]

Plasma cell leukemia is associated with a poor prognosis, with a shorter survival than that of patients presenting with typical multiple myeloma. Clinical distinctions that have been reported between the two forms of multiple myeloma include a younger age, a higher prevalence of hepatosplenomegaly and lymphadenopathy, thrombocytopenia, a lower serum M protein level, extramedullary involvement, and renal failure when leukemia is present.[4] The median age of patients with plasma cell leukemia in the SEER database was 67 years, essentially no different from that of the patients with multiple myeloma, suggesting that referral bias exists both for patients reported from the Mayo Clinic as well as in a transplant registry, which would receive referrals of younger patients for treatment.

The control mechanisms under which plasma cells initially remain confined to the bone marrow and then ultimately enter the circulation are not well understood. The malignant cells in the peripheral blood can be easily identified morphologically and their presence can be confirmed by flow cytometric evaluation demonstrating strong reactivity with CD38 and CD138. Despite these technological advances, when samples from two patients with plasma cell leukemia were blindly submitted to laboratories in the UK, only 51% of the laboratories diagnosed both samples correctly as plasma cell leukemia.[5]

The surface phenotype of plasma cells in plasma cell leukemia is different from that of bone marrow plasma cells in patients with multiple myeloma: CD9, HLADR, CD117, and CD20 are differentially expressed in circulating plasma cells compared with bone marrow plasma cells in myeloma patients. Increased levels of soluble CD95 have been observed in plasma cell leukemia. The plasma cells that circulate do not appear to express CD56. The lack of (or weak) expression of CD56 is a characteristic feature of plasma cell leukemia and delineates a special subset of myeloma patients at diagnosis.[6]

Significant genomic differences between plasma cell leukemia and myeloma have been recognized. Patients with plasma cell leukemia have shown gains in 1q compared with patients with multiple myeloma. Among four patients with plasma cell leukemia, three had monosomy of the *RB1* locus and one had a mono-allelic deletion of the *P53* gene. *NRAS* and *KRAS* were found in 50% of plasma cell leukemias. Among 14 patients with plasma cell leukemia, chromosomal abnormalities were detected in all, with deletion of 13q in 78% and *P53* deletion in 43%. Translocations at the immunoglobulin heavy chain locus on chromosome 14 were found in 56%. In an IFM study of 40 patients with primary plasma cell leukemia, informative karyotypes were obtained for 34; 23 showed complex hypodiploid or pseudodiploid karyotypes; 68% had monosomy 13, which may account for the poor prognosis of patients with plasma cell leukemia.[7]

Genetic and clinical data were recently reported for 80 patients with plasma cell leukemia and compared to those of a cohort of 439 patients with multiple myeloma. Among the 80 patients, 39 had secondary plasma cell leukemia and 41 had primary plasma cell leukemia. As expected, patients with secondary plasma cell leukemia developing circulating cells at the point of progressive disease had a median survival of 1.3 months. Forty-two percent of patients with secondary plasma cell leukemia were hypodiploid, 42% pseudodiploid, and 17% hyperdiploid. Translocations of the immunoglobulin heavy chain locus 14q32 were highly prevalent in secondary and primary plasma cell leukemias (82% and 87%, respectively). In primary plasma cell leukemia, IgH translocations involve

exclusively 11q13, while in secondary plasma cell leukemia, multiple partner oncogenes are involved. Both primary and secondary plasma cell leukemias show inactivation of *TP53*, a genetic abnormality known to be associated with poor prognosis and short survival.[8,9] Although novel agent chemotherapy can overcome some adverse genetic abnormalities associated with multiple myeloma, such as t(4;14), novel agents have not been seen to have any impact on outcome in patients who have *TP53* inactivation.[10]

In a study of 11 plasma cell leukemia patients, all showed clonal chromosomal abnormalities. Chromosomes 1, 8, 13, and 16 showed the highest number of copy number alterations with 8q24 being the chromosomal region most frequently involved. In eight of 12 patients, abnormalities that directly targeted or were very close to *MYC* were found. These abnormalities were associated with increased levels of *MYC* mRNA. *MYC* deregulation is one of the major molecular events in the oncogenesis of plasma cell leukemia.[11]

The prognosis of patients with plasma cell leukemia treated with conventional therapy has been reported with median survivals of 7 to 14 months for those with primary plasma cell leukemia and 2 to 7 months for those with secondary plasma cell leukemia. Intermediate doses of melphalan and dexamethasone have been reported to be superior to vincristine, doxorubicin, and dexamethasone for treatment.[12] Among 15 patients who underwent stem cell transplantation and were reported to the International Bone Marrow Transplant Registry, there were three long-term survivors (1 autologous, 2 allogeneic).[13] Clearly, stem cell transplantation can play a role in the management of plasma cell leukemia, but responses would not be anticipated to be durable, and further post-transplantation therapy would be required.

The role of novel agents in the treatment of plasma cell leukemia remains undefined. In a study of five patients with plasma cell leukemia, thalidomide did not result in a response in any.[14] However, in another study, four thalidomide-treated patients with plasma cell leukemia had a median reduction in M protein of 80%, one achieving a very good partial response.[15] Lenalidomide has been reported to be effective for the treatment of plasma cell leukemia as a single agent and in combination with melphalan and prednisone.[16,17]

Bortezomib treatment for plasma cell leukemia has led to the restoration of normal peripheral blood counts and elimination of transfusion dependency.[18] Three patients with primary plasma cell leukemia and high risk cytogenetics had an excellent response to bortezomib and dexamethasone and sustained remission.[19] Other single-case reports on the effectiveness of bortezomib and dexamethasone for plasma cell leukemia have been published.[20] Among 12 patients with plasma cell leukemia who received bortezomib, five achieved partial responses, four very good partial responses, and two complete responses for a response rate of 92%. Eight of the patients were alive 6 to 21 months after treatment with bortezomib suggesting that this agent has particular effectiveness.[21]

Thirty-one patients with plasma cell leukemia were treated with novel agents. The overall response rate was 70% (17/24), including 11 complete responses or very good partial responses (45%). Bortezomib-containing regimens provided the best response rates. The median progression-free survival was 8 months (range, 0-26) and the median overall survival was 15 months (range, 6-108). Comparing this survival with that described for patients reported before 1999, it can be seen that the use of novel agents has improved the survival of patients with plasma cell leukemia.[22]

It appears that the prognosis in patients with plasma cell leukemia will continue to improve with the combination of novel agents and high-dose therapy. Novel agents seem to have the potential to overcome some of the adverse genetic and immunophenotypic characteristics that these patients have.

A summary of treatment regimens available for plasma cell leukemia is given in Table 1.

Table 1. Therapy for plasma cell leukemia.

Regimen (N. treated)	Median overall survival (months)	Reference
Autologous stem cell transplantation (n=272)	25.7	1
Conventional therapy (n=41)	11.2	9
Thalidomide-dexamethasone (n=12)	N/A	15
Lenalidomide (n=1)	N/A	16
Bortezomib (n=3)	Response duration 14+, 21+, 27+	19
Novel agents (n=31)	15, PFS 8	22

N/A, not available; PFS, progression-free survival.

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