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Plasma Cell Neoplasms

Raymond Alexanian, M.D.

Plasma cell neoplasms constitute a group of entities with marked variations in clinical manifestations, extent of disease, frequency and severity of complications and treatment requirements. These disorders are usually associated with increased production of a homogeneous globulin, recognized as a "peak" on serum or urine electrophoresis. Multiple myeloma is the most common plasma cell neoplasm, and must be distinguished from other closely related disorders such as localized plasmacytoma, asymptomatic and indolent myeloma, idiopathic "peaks" and macroglobulinemic lymphomas. Plasma cell dyscrasias may be classified in the following manner:

Disorder	Approximate frequency (Percent)
Plasma cell myeloma	
Multiple myeloma—symptomatic	65
Multiple myeloma— asymptomatic and indolent	2
Localized plasmacytoma	5
Idiopathic peak	20
Macroglobulinemia of Waldenstrom	8
Heavy-chain diseases	< 1
Primary amyloidosis (without overt myeloma)	< 1

Localized Plasmacytoma

About five percent of patients with plasma cell neoplasms have evidence of only one or two plasmacytomas, without the major complications frequently associated with multiple myeloma. In these patients, myeloma proteins are low or absent and the serum concentration of nonmyeloma immunoglobulins is generally normal. Local radiotherapy to about 4,000 rads is usually effective. Such therapy may reduce the level of any myeloma protein present and elevate the serum concentrations of nonmyeloma immunoglobulins to supranormal levels, indicating that a large fraction of tumor has been eliminated.¹ This elevation of normal immunoglobulins also suggests that a small number of malignant cells may have inhibited normal immunoglobulin production by means of a humoral mechanism.² Clinical stability may be sustained for many years.

However, some patients thought to have localized plasmacytomas soon develop rising myeloma proteins, pointing to an incorrect disease classification at diagnosis and the need for chemotherapeutic management. The median survival for a group of patients with no

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more than two plasmacytomas was about eight years.¹

Asymptomatic and Indolent Myeloma

Rare patients with unequivocal multiple myeloma are asymptomatic; the diagnosis is then made by a bone marrow examination following a coincidental serum electrophoresis or the detection of mild anemia. Generally, there is a large IgG peak, greater than 3.0 grams percent, with depression of normal IgA and IgM immunoglobulins. Indolent myeloma must be differentiated from "idiopathic peaks" by the demonstration of anemia due to bone marrow plasmacytosis, marked depression of normal immunoglobulins or lytic bone lesions. As long as the disease remains asymptomatic and the myeloma protein level does not increase, these patients may be followed without chemotherapy. Vertebral compression fractures or recurrent infection indicate the need for therapy. Long-term stability of both symptomatology and myeloma protein production may occur in patients with indolent myeloma, as in those with only one or two localized plasmacytomas. For reasons not yet clarified, the plasma cells in these patients have a low growth fraction, and the possibility of a superior immunosurveillance capacity must be evaluated. The median survival for a group of patients with indolent myeloma was about five years. In one-half of the patients, chemotherapy was not required for at least two years.¹

Idiopathic Monoclonal Gammopathy

Idiopathic peaks have been identified in the serum of about 0.5 percent of normal individuals over 30 years of age.³ These patients have no symptoms attributable to myeloma and serum electrophoresis was usually ordered to evaluate another disorder. In one large series, about 90 percent of the abnormal protein spikes were of IgG type, with a serum concentration always less than 3.0 grams per-

cent.¹ Normal immunoglobulins were not depressed, lytic bone lesions were not present and Bence Jones proteins were absent. A bone marrow examination is usually not required in patients with idiopathic monoclonal gammopathy of IgG or IgA type. Idiopathic peaks of IgM type are rare, as most of these patients have an underlying lymphoma or chronic lymphocytic leukemia.⁴ The frequency of IgG or IgA peaks in patients with cancer was similar to that in a normal population of the same age; control of the cancer did not effect the level of the peaks.⁵ Thus, the relationship of serum peaks to cancers other than myeloma or macroglobulinemia is probably coincidental. The concentration of monoclonal globulin usually remains stable for many years and evolution into overt myeloma rarely occurs. Chemotherapy is not indicated unless there is evidence of an increasing mass of plasma cells. The lifespan of patients with this chemical abnormality depends on their age and the primary condition under evaluation at the time of discovery.

Multiple Myeloma

Multiple myeloma is a disseminated neoplasm of plasma cells frequently characterized by bone destruction, bone marrow failure and the production of unique immunoglobulins. (Fig. 1.) About 96 percent of patients show evidence of globulin peaks on serum or urine electrophoresis.

Supportive and Ancillary Therapy

These patients may have a variety of disease complications that must be managed concomitantly with chemotherapy for the myeloma. Back pain due to compression fractures of the thoracic or lumbar spine, constitutes the most common presenting symptom. Increased physical activity should be expedited with the rational use of analgesics, corsets and walkers. Back braces are often not well

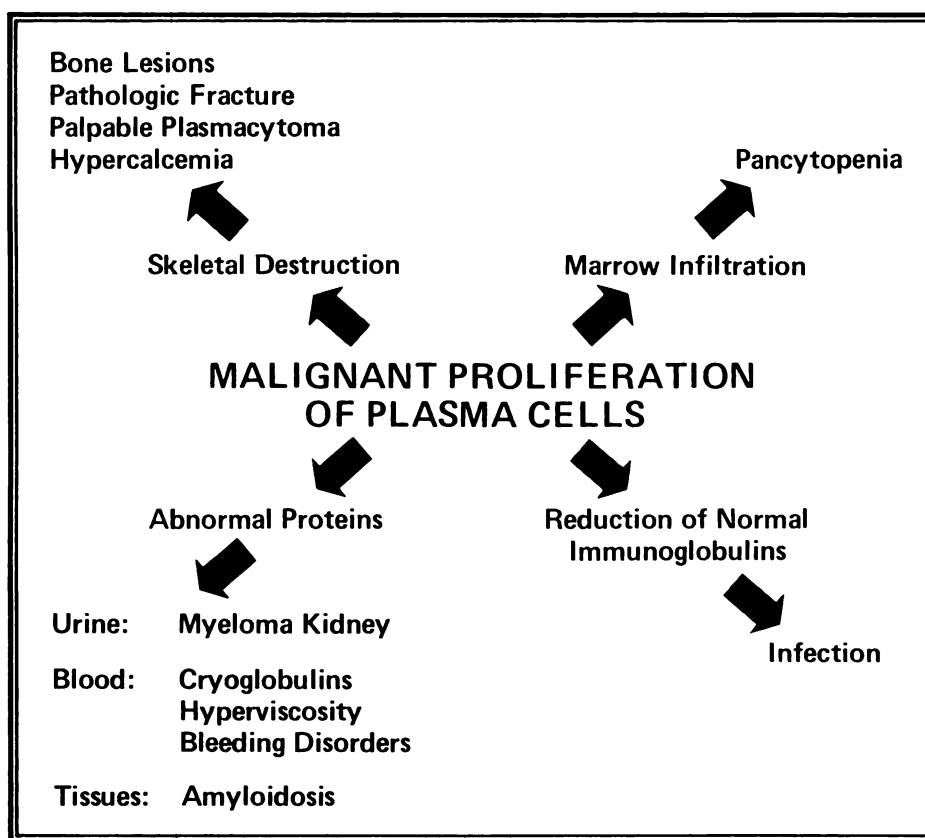


Fig. 1. Common complications in multiple myeloma.

tolerated. Radiation therapy is useful for disabling bone pain from pathologic fractures and is recommended for severe pain persisting after the first course of chemotherapy. Prompt radiotherapy to areas of cord compression will prevent the need for decompressive laminectomy. Corticosteroids help prevent edema if emergency radiation therapy is administered to the spinal cord. Internal surgical fixation of long bone fractures assists in reducing pain and allowing ambulation. Sodium fluoride and calcium continue to be under study for their role in increasing bone calcification and reducing bone pain.

Certain metabolic complications must also be prevented or treated. • Dehydration must be avoided and adequate hydration is essential, since myeloma pa-

tients frequently have high calcium levels and increased excretion of Bence Jones protein. • Hypercalcemia must be managed vigorously and is usually controlled by a high fluid intake, increased physical activity, diuretics and corticosteroids. In previously untreated patients, alkylator-prednisone therapy should not be delayed since it almost always reverses hypercalcemia. In disabled patients with drug-resistant myeloma, control of hypercalcemia is less likely, but Mithramycin may provide brief relief. • Hyperuricemia is managed by allopurinol. Short-term hemodialysis may be useful for severe renal failure, either due to "myeloma kidney" or amyloidosis; long-term hemodialysis has been continued in some patients with chronic uremia in remission. • Symptomatic

Table 1.
Multiple Myeloma –
Response Rates in Melphalan
Treatment Programs

Treatment	No. Treated	Response Rate Percent Evaluable	Median Survival (months)
Daily melphalan	23	14	15*
Intermittent melphalan	54	31	17
Intermittent melphalan + prednisone	132	59	22
Intermittent melphalan + prednisone + procarbazine	226	53	22
Intermittent melphalan + prednisone + procarbazine + vincristine	124	59	30

*A large fraction of these patients were subsequently treated with intermittent melphalan-prednisone when no response to daily melphalan was apparent.

anemia is treated with packed red cell transfusions; androgens may be used in selected patients with chronic anemia who have adequate iron supply. • Infection has not been successfully prevented with prophylactic gamma globulin.

Evaluation of Remission

Serial evaluations of myeloma protein levels are required to determine the effect of chemotherapy on tumor mass. Changes in myeloma protein production rate are calculated from: the myeloma protein concentration; the changing catabolic rate as related to the concentration of IgG proteins;⁶ the assumed or measured plasma volume.² Simple computer programs permit the rapid calculation of tumor mass change in individual patients.² In the Southwest Oncology Group, reduction to less than 25 percent of the pretreatment serum myeloma protein production rate (considered as 100

percent) indicates a "response," a fall to 25-50 percent signals "improvement," and a reduction to only 50-100 percent of the initial value denotes "no response." The level of abnormal serum protein is most precisely assessed by routine electrophoresis. Radial immunodiffusion measurements are helpful in evaluating tumor mass change only in those patients with marked reductions in IgA peaks. More sensitive techniques are needed to measure low myeloma protein levels in those 15 percent of treated patients with an apparent disappearance of the serum peak.

For patients with only Bence Jones protein excretion, the disappearance of abnormal protein is required to confirm a "response." Bone marrow differentials of plasma cell percentage are of little value in assessing tumor mass change because of their low precision, compared to abnormal protein quantitations,

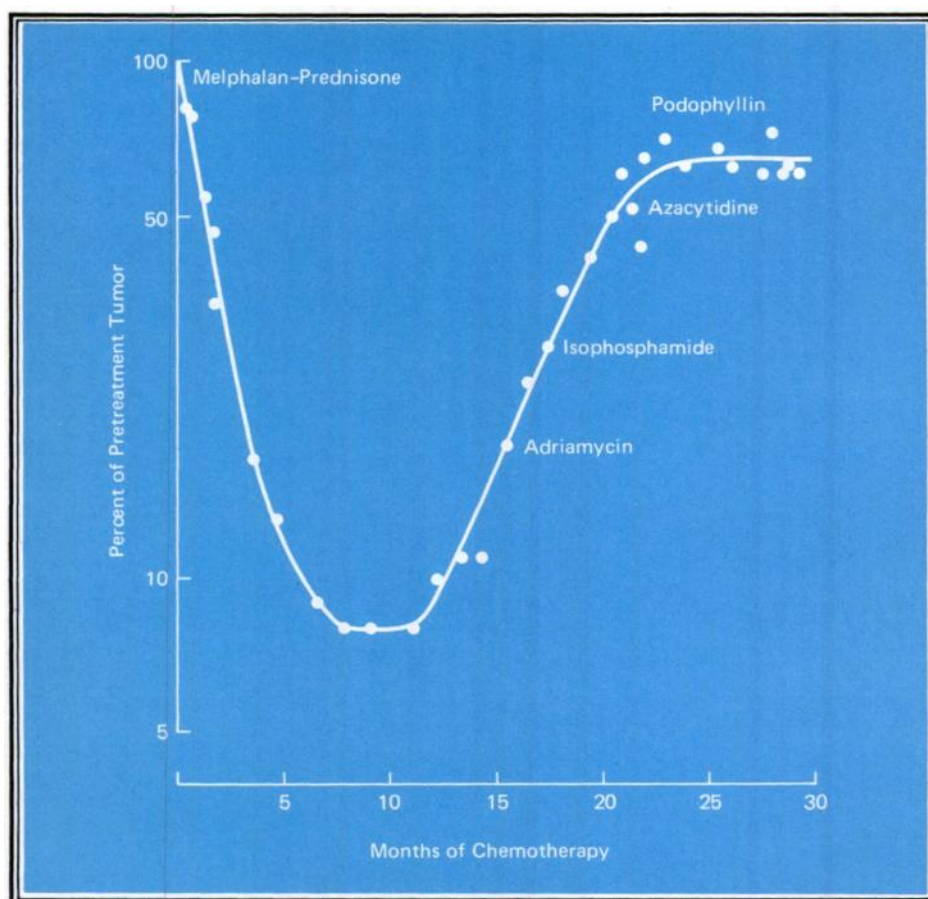


Fig. 2. Serial changes in tumor mass in a patient receiving intermittent courses of melphalan-prednisone. Plateaus in tumor mass were evident during remission and shortly before death.

and their poor correlation with other disease parameters. Clinical responses are usually of good quality and patients are able to resume most of their normal activities.

Unless there is persistent renal failure, the hemoglobin value increases to more than 10 grams percent; some patients also develop recalcification of lytic bone lesions⁷ or recovery of depressed normal immunoglobulins.⁸ Nephelometric studies of serum have recently provided automatic and reproducible assessments of normal immunoglobulin concentration in these patients.

Chemotherapy (Remission Induction)

In 1958, Russian investigators reported that phenylalanine mustard was useful in myeloma. Clinical trials were initiated with the L-isomer of this drug (melphalan), and an intermittent schedule in maximal doses was evaluated by Bergsagel at M.D. Anderson Hospital, in collaboration with other members of the Southwest Oncology Group (SWOG). Bergsagel reported that disease remissions were achieved in a large fraction of patients and significant survival prolongation first became evident.⁹

Between 1965-1972, the Southwest Oncology Group treated 559 patients

with multiple myeloma using one of several melphalan treatment programs in a series of controlled studies.*¹⁰⁻¹² Response rates and median survival times are summarized in Table 1. A higher frequency of response resulted from an intermittent melphalan schedule, compared to a daily schedule, even though the total dose over a specific period was similar. The use of melphalan and prednisone in combination enhanced the response rate even further, so that about 55 percent of patients with evaluable trials achieved a 75 percent reduction in tumor mass. Serial changes in calculated

... intermittent courses of melphalan and prednisone repeated at four-week intervals with periodic vincristine injections appears to provide the best initial treatment for patients with multiple myeloma.

tumor mass in a patient responding to melphalan-prednisone are shown in Fig. 2. Progressive relapse occurred despite continued therapy that included various investigational drugs.

From 1968-1972, the value of adding procarbazine and vincristine to the melphalan-prednisone regimen was studied. Procarbazine alone was active in several untreated myeloma patients; vincristine also reduced tumor mass, as shown by the further reduction of small myeloma protein peaks in some responsive patients. Unfortunately, there was no further elevation of response rates following the addition of procarbazine and vincristine to the melphalan-prednisone combination. Although the use of procarbazine did not improve survival, the quadruple drug combination, including

both procarbazine and vincristine, was associated with the longest median survival time observed to date in patients with multiple myeloma (i.e., 30 months).¹²

Thus, intermittent courses of melphalan and prednisone repeated at four-week intervals with periodic vincristine injections appears to provide the best initial treatment for patients with multiple myeloma. (Melphalan, 10 mg./m.²/day concurrently with prednisone, 60 mg./m.²/day for four days, and vincristine, 1 mg. intravenously every 14 days. Dose adjustments are made in accordance with blood counts and patient tolerance.) Other SWOG treatment combinations, that include adriamycin and cyclophosphamide are currently under evaluation for remission induction in these patients.

Chemotherapy (Remission Maintenance)

The Southwest Oncology Group conducted the first study on remission maintenance for multiple myeloma between 1969-72.^{12,13} Ninety-eight consecutive patients in remission after at least 12 months of chemotherapy were assigned to treatment regimens either with: (A) continued melphalan-prednisone; (B) 1,3-Bis (2-chloroethyl)-1-nitrosourea (BCNU)-prednisone; or (C) no chemotherapy. More than 30 patients were placed in each maintenance group; more than 50 percent of each group have died. (Fig. 3.) Responding patients receiving indefinite melphalan-prednisone or BCNU-prednisone had a higher frequency of pneumonia and herpes zoster. Patients relapsing without any chemotherapy had a high incidence of second remissions with resumption of melphalan-prednisone, but no patient relapsing on the BCNU-prednisone program responded to melphalan-prednisone. These results suggested that continued, indefinite alkylating agent chemotherapy after the first year may be more harmful than

*In addition to the author, the following medical centers and investigators participated in the SWOG trials summarized here, registering more than 75 percent of the patients: University of Arkansas Medical Center, Little Rock (Dr. A. Haut); Cleveland Clinic Foundation, Cleveland (Dr. J. Weick); Henry Ford Hospital, Detroit (Dr. R. Monto); Ohio State University College of Medicine, Columbus (Dr. S. Balcerzak); Scott and White Clinic, Temple (Dr. J. Bonnet).

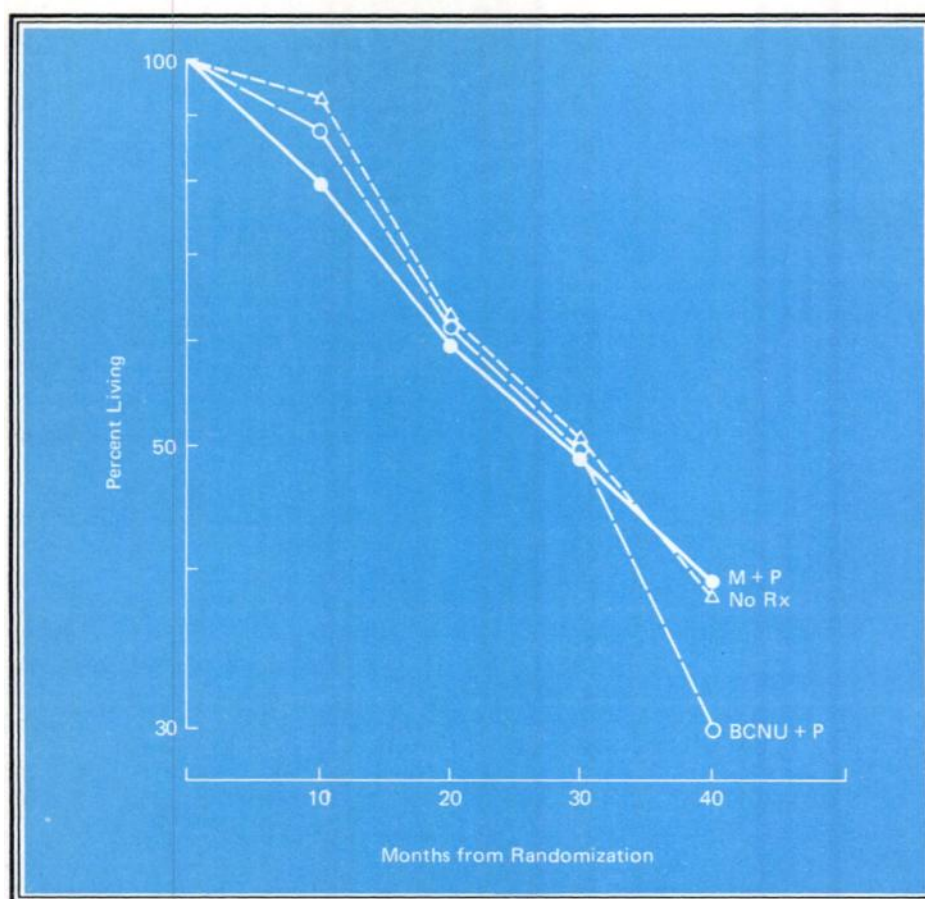


Fig. 3. Survival of randomized responsive patients maintained after the first 12 months on continued melphalan-prednisone (solid line), BCNU-prednisone (open circles), or no chemotherapy (dashed line).

helpful to myeloma patients in remission. A similar conclusion may apply to myeloma patients who are clinically stable but who have not responded in accordance with the SWOG myeloma protein criteria. Nevertheless, these studies justified the evaluation of other drugs during remission in order to reduce tumor mass maximally. Unfortunately, no further reduction occurred in myeloma protein peaks with cytosine arabinoside, methotrexate and hydroxyurea, although only modest doses were used in the ambulatory patients that were treated. Other maintenance treatment combinations are being evaluated by the SWOG, including azathioprine, BCG,

BCNU and vincristine. Preliminary results are encouraging and a median survival time of almost three years is projected for currently treated patients.

Thus, patients who achieve a 75 percent reduction of myeloma proteins should not receive indefinite alkylating agent treatment since their clinical course appears to be just as stable without any chemotherapy. This may lead to improved immunocompetence in preventing both infection and tumor relapse. Reinduction therapy with melphalan-prednisone-vincristine is indicated for patients on unmaintained remissions when a significant increase in myeloma protein level becomes evident.

In myeloma patients resistant to melphalan-prednisone, numerous drugs have been evaluated by the SWOG and found inactive, such as BCNU, cyclophosphamide, podophyllin derivatives and vinca alkaloids. Adriamycin-prednisone was effective in about 15 percent of patients and one patient responded to bleomycin. (This individual excreted 15 grams/day of Bence Jones protein despite six months of intermittent melphalan-prednisone in maximal doses. After the administration of a total of 90 mg. bleomycin, abnormal protein disappeared from the urine for 12 months only to reappear and increase shortly before death.)

Prognosis

Marked variability in disease manifestations, clinical course and sensitivity to chemotherapy have prevented an accurate estimate of prognosis in individual patients. No major disease parameters effecting the likelihood of remission have been identified, but several factors have now been shown to influence survival time. Thus, increasing degrees of anemia, hypercalcemia and renal failure are associated with progressively shorter lifespan. Very old patients and those producing IgA monoclonal proteins have a poorer prognosis than other patients. Early death, within one month after the first course of chemotherapy, still occurs in four percent of patients.

An assessment of prognosis must consider the myeloma tumor mass before chemotherapy and the magnitude of tumor reduction after treatment. The absolute number of plasma cells in patients with myeloma may be derived from the relationship between the in vitro production rate of globulin per cell² and the in vivo turnover rate of myeloma globulin in the plasma.⁶ Salmon has calculated that the "average" patient with multiple myeloma has about 10^{12} cells/m.² This number is probably reached within three years, during which time there is pro-

gressive slowing of the growth rate with increasing tumor mass.¹⁴ The extent of disease may also be assessed by a combination of routine laboratory tests. The following represents a simple system now used in myeloma patients treated by the Southwest Oncology Group:^{15,16}

High tumor mass ($>1.2 \times 10^{12}$ plasma cells/m.²) Confirmed when <i>any</i> of the following is present: 1. Hemoglobin <8.5 gms. percent. 2. Corrected calcium >11.5 mg. percent.* 3. Serum IgG peak >7 gms. percent or IgA peak >5 gms. percent. 4. Extensive lytic bone lesions
Low tumor mass ($<0.6 \times 10^{12}$ plasma cells/m.²) Confirmed when <i>all</i> of the following are present: 1. Hemoglobin >10.5 gms. percent. 2. Corrected calcium <11.5 mg. percent.* 3. Serum IgG peak <5 gms. percent or IgA peak <3 gms. percent. 4. None or few lytic lesions.
Intermediate tumor mass ($0.6-1.2 \times 10^{12}$ plasma cells/m.²) All other patients who do not qualify for high or low tumor mass.
*Corrected calcium (mg./100 ml.) = serum calcium (mg./100 ml.) - serum albumin (g/100 ml.) + 4.0

In a large number of myeloma patients treated by the SWOG with alkylator-prednisone combinations between 1965-1972, about 45 percent had a "high" mass, about 30 percent an "intermediate" mass, and about 25 percent a "low" mass. The response rate ranged from 50-60 percent for patients in each group who received adequate trials, indicating that when large numbers of patients are considered, there is a constant fractional cell-kill regardless of the absolute cell number.¹⁶

Both the pretreatment tumor mass grade and the degree of remission had a major influence on prognosis.¹⁶ Survival times were longest for those patients with lower numbers of plasma cells and proportionately shorter for those with a larger tumor mass after an optimum treatment regimen of melphalan-prednisone. (Table 2.)

Other studies have shown that the prolongation of survival in responding patients can be accounted for by the duration of remission.¹⁷ These observations not only provide a more valid prognosis for individuals, but also form the basis for stratifying patients into different SWOG treatments according to tumor mass. In addition, they emphasize the importance of achieving a maximal reduction in absolute numbers of malignant cells.

Cell Kinetics

In most patients responding to melphalan-prednisone chemotherapy, an approximate one-log reduction in cell number has been associated with a short plateau phase, preceding eventual relapse of a resistant cell population. (Fig. 2.) During the period of remission, the fraction of plasma cells labelled in vitro with tritiated thymidine usually increases.^{18,19}

The change from a median 2.5 percent for untreated patients to a median five percent for patients in remission suggested that an increased growth fraction had developed. These findings sup-

ported the concept that progressive tumor growth was associated with a steadily declining proliferating fraction.

The kinetics of tumor mass change following chemotherapy were analyzed by assuming the presence of varying proportions of "drug-sensitive" and "drug-resistant" cells. Thus the median half-time was about one month for the elimination of sensitive cells, as calculated from the kinetics of initial tumor reduction in responding patients. In most cases, the entire population of sensitive cells would be eliminated within three years, assuming a constant exponential rate of cell destruction. Therefore, the duration of maintenance or reinforcement treatments with alkylating chemotherapeutic agents could be individualized from the initial rate of tumor reduction.

The clinical course of Waldenstrom's macroglobulinemia is highly variable with about 20 percent of patients not requiring chemotherapy for long periods.

After a maximum tumor reduction had been achieved with chemotherapy, responding patients showed varying durations of a stable plateau in cell number. Most had evidence of relapse after less than one year of stability, due primarily to the emergence of a resistant tumor population with a median doubling time, during the early phases of relapse, of about two months. This figure was much shorter than the six to 12 months calculated by Hobbs²⁰ and was consistent with the short evolution of human myeloma as suggested by Salmon.^{2,14}

Of interest is that most patients observed during relapse failed to demonstrate a slowing phase of tumor growth before death. This emphasized the marked variability in tumor growth; some tumors with a high mass continued to grow rapidly while others with a low mass (localized or indolent) remained

Table 2.
Effect of Pretreatment Tumor Mass
on Survival and Remission*

Degree of Remission**	Tumor Mass Grade		
	High	Intermediate	Low
All patients	17	27	39
Unresponsive			
50-100	9	13	27
25-49	14	22	34
Responsive			
10-24	17 (8)	25 (9)	40 (21)
< 10	33 (21)	34 (24)	46 (32)***
* Each figure indicates median survival for all patients/group, with parentheses indicating median remission duration for responders. ** Percent of control for serum peaks only. *** All patients in this group showed disappearance of their serum peak.			

stable or showed slow growth for prolonged periods.¹ One can only speculate on the role of immunosurveillance or other factors in the regulation of growth patterns.

Macroglobulinemia of Waldenstrom

Waldenstrom's macroglobulinemia, a chronic lymphoproliferative disorder, may cause lymph node enlargement, bone marrow infiltration by pleomorphic lymphoid cells and hepatosplenomegaly. All patients have an increased production of a monoclonal gamma globulin of IgM type. The major clinical and laboratory features of Waldenstrom's macroglobulinemia are demonstrated in Fig. 4. Since the lymphocytes of patients with chronic lymphocytic leukemia or certain lymphomas usually show

evidence of monoclonal IgM production, these disorders should also be considered a monoclonal gammopathy of bone marrow-derived lymphocytes. In about four percent of patients with lymphoma and diffuse histologic infiltration of lymph nodes, the production rate was so high that a monoclonal IgM peak was confirmed on serum electrophoresis.⁴ The clinical course of Waldenstrom's macroglobulinemia is highly variable with about 20 percent of patients not requiring chemotherapy for long periods. Immunological manifestations, such as increased cold sensitivity or autoimmune hemolytic anemia, may dominate the clinical course.

Treatment of Complications

As with multiple myeloma, optimum

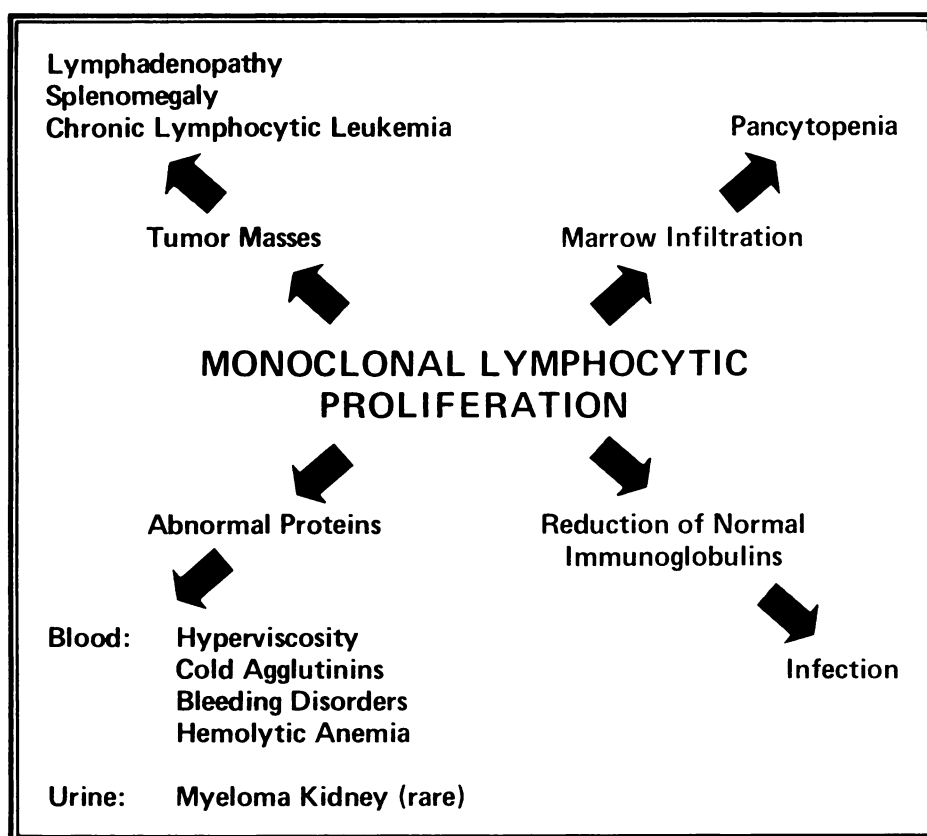


Fig. 4. Common complications in monoclonal macroglobulinemia.

management includes the simultaneous control of complications and the reduction of tumor mass with chemotherapy. A hyperviscosity syndrome that may produce neurologic symptoms or an increased bleeding tendency requires prompt plasmapheresis. This may be conducted rapidly and efficiently with an IBM separator. Symptomatic levels of hyperviscosity are uncommon unless monoclonal IgM peaks exceed five gm. percent. Anemia may require packed red cell transfusions, but a markedly increased plasma volume may account for much of the apparent reduction in hemoglobin or hematocrit. Hypercalcemia is rare since skeletal lesions are uncommon; because the degree of Bence Jones proteinuria is usually low, renal failure is also infrequent. Patients with macro-

globulinemia usually do not have as marked a depression of normal immunoglobulins as those patients with multiple myeloma.

Chemotherapy with intermittent courses of leukeran and prednisone in maximally tolerated doses will reduce tumor mass by more than 50 percent in about 80 percent of adequately treated patients.⁴ (Chlorambucil is initiated in a dose of 8 mg./m²/day concurrently with prednisone, 40 mg./m²/day for 10 days, and repeated at six to eight week intervals. Dose adjustments are made according to blood counts and patient tolerance.)

Evaluation of Response

Evaluation of remission is based primarily on changes in monoclonal ma-

croglobulin production rate. As in multiple myeloma, serial determinations of the serum concentration of abnormal globulin and of measured plasma volume provide the most precise index of tumor mass reduction. Serial evaluations of lymph node size, blood lymphocyte count and hemoglobin concentration are also helpful. Control of these overt clinical manifestations will usually occur with only a 50 percent reduction in tumor mass, as assessed from the protein data.⁴ Thus, "complete" remissions in chronic lymphoid cancers occur with relatively slight tumor reductions, emphasizing the need for more effective treatment of these disorders. The utility of other drug combinations must be evaluated in responding patients who have achieved a maximum reduction of tumor mass. The median survival time for a group of patients with macroglobulinemia was about three years,⁴ similar to survival of patients with multiple myeloma.

Perspectives for Patient Care

Plasma cell neoplasms are no longer considered rare diseases, and increasing numbers of patients are now being recognized. Optimum management requires close collaboration between the private physician and a referral center familiar with this group of disorders. Specialized studies such as immunoelectrophoretic typing, serial quantitation of normal and abnormal immunoglobulins and precise calculations of tumor mass change contribute substantially to improved patient care. A high frequency of tumor response, marked degrees of remission and remissions of long duration provide a better opportunity for longer survival times of good quality for many patients. Optimum control of initial complications, rational therapy for advanced and remission phases of disease, as well as the development of new chemotherapeutic agents for the treatment of relapsing patients with tumor resistance are essential. ©

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