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Melphalan Therapy for Plasma Cell Myeloma

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UNTIL RECENTLY, chemotherapy for multiple myeloma has been disappointing. Synthesis of 3-{p-[bis-(2-chloroethyl)amino]phenyl}L-alanine (melphalan) by Bergel and Stock[1] in 1953 and of the DL-form (sarcolysin) by Larionov et al.[2] in 1955 was followed in 1958 by the application of sarcolysin in plasma cell myeloma by Blokhin et al.[3] Numerous investigators have since used melphalan for myeloma patients, with objective improvement in 15[4] to 85 per cent.[5] This varied response rate reflects differences in patient selection, assumed duration of adequate treatment trial, and criteria used for evaluation of response.

This report documents the incidence of objective improvement and survival time in 82 consecutive patients with plasma cell myeloma treated with melphalan* at one institution during a 7-year period. Certain disease parameters, particularly the level of serum and urine myeloma protein, were examined in detail before and after institution of therapy in order to identify those features that provided more precise criteria for assessing the incidence, degree, and duration of clinical response.

METHODS OF STUDY

All patients with plasma cell myeloma treated with melphalan at The University of Texas M. D. Anderson Hospital and Tumor Institute between June 1, 1959 and December 1,

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1966 are included in this report. Forty-four (54 per cent) were male; 17 (21 per cent) were Negro. The median age at the time of diagnosis was 60 years, ranging from 33 to 83 years. The 60–69-year age group was the largest; 14 patients (17 per cent) were less than 50 years.

Laboratory Studies

Diagnosis was based on the demonstration of bone marrow plasmacytosis. Plasma cells constituted more than 10 per cent of the cellularity in all aspirated specimens used for diagnosis. Roentgenograms of all patients showed skeletal lesions consistent with myeloma; these changes were followed serially after beginning therapy. Electrophoresis was done initially using the Beckman Model R paper electrophoresis system and later on cellulose acetate using the Beckman Model R-100 microzone system. When present in serum, the concentration of myeloma globulin was calculated (grams per cent) and measured serially after institution of melphalan. A qualitative test for urine protein was performed with sulfosalicylic acid in all subjects. When positive, the presence of light chain (Bence Jones) myeloma protein was established by electrophoresis and/or immunoelectrophoresis[6] of a concentrated urine specimen. Urine protein excretion (grams/day) was measured serially following melphalan treatment after electrophoresis had established that virtually all of this material represented Bence Jones protein. Each determination of serum myeloma globulin concentration and urine protein excretion was expressed as a percentage of the pretreatment level. Hemoglobin, white blood count and differential, platelet count, blood urea nitrogen, and serum calcium measurements were performed in all subjects, and repeated at appropriate intervals. Chemotherapy with other drugs, found subsequently to be ineffective in plasma cell myeloma, was given to 23 patients between diagnosis and melphalan treatment. Concomitant short-term therapy with corticosteroids for hypercalcemia and localized radiotherapy for symptomatic bone lesions were given when indicated.

Melphalan Dosage

In initial studies (14 patients), 0.2 mg./Kg. of body weight/day of melphalan was given until significant leukopenia (white blood cell count less than 3000/ml.^{3}) or thrombocytopenia (platelet count less than 100,000/mm.^{3}) was apparent. Most patients receiving this dosage had severe cumulative bone marrow toxicity.[7] A less toxic intermittent dosage schedule of 0.7–1.3 mg./Kg. of body weight, administered in 4 days at approximately 6-week intervals, was given to the following 68 patients. This dose was given despite azotemia, and was not reduced for leukopenia or thrombocytopenia if these changes were due to marrow infiltration by plasma cells. Melphalan dosage level was adjusted to produce either mild leukopenia or thrombocytopenia *(vide supra)* 3–4 weeks later. With this schedule, marrow function usually recovered within six weeks; serious toxicity or unusual side effects were infrequent and minimal in severity. In most cases, treatment was continued at regular intervals until death. All patients who received a single course of melphalan were included in the survival analysis.

Criteria for Evaluation of Response

Response was evaluated at least 3 months after beginning melphalan therapy according to criteria recommended by the Chronic Leukemia-Multiple Myeloma Task Force,[8] and defined as one or more of the following changes in a direct manifestation of disease for at least 2 months: (1) decrease in serum myeloma protein concentration or urine myeloma protein excretion to less than 50 per cent of the pretreatment value, (2) more than 50 per cent regression in the product of the two largest diameters of plasmacytomas, and (3) radiographic evidence of skeletal healing. Response could not be determined in 14 patients; in 3, no myeloma protein or plasmacytoma was detected; in 5, data was incomplete. Six subjects died within 3 months of the start of therapy; these cases were considered not evaluable because most responding patients required 3 months before suppression of their serum myeloma concentration to less than 50 per cent of the pretreatment value (*vide infra*). The effect of these 6 "early deaths" on survival was evaluated separately.

Table 1.—*Correlation of Improvement in Clinical Parameters with Response to Melphalan*

(Number of patients with abnormally corrected/total abnormal)

	Responsive	Unresponsive	Not evaluable
No. of patients	40	28	14
Symptomatic disability*	25/27	7/21	3/11
Plasmacytoma	6/6	0/4	0/0
Anemia (<10 Gm.%)†	17/20	2/14	0/3
Hypoalbuminemia (<3.0 Gm.%)‡	14/16	1/6	0/3
Azotemia (BUN >30 mg.%)	8/10	0/3	1/3
Bone recalcification	5/40	0/28	0/14

*Improvement > 20 units with pretreatment performance < 80 units on Karnofsky scale (9).
†Increase > 2 gm.%.
‡Increase > 1 gm.%.

Results

Frequency of Response

Of 82 patients treated with melphalan, 40 (49 per cent) had an objective response. In the 68 evaluable cases, the response rate was 59 per cent. In addition to the parameters defining response, improvement occurred in other manifestations of disease in responding patients (Table 1). When present and not related to old pathologic fractures, bone pain usually diminished and impaired performance status improved in almost all responding patients. Significant symptomatic improvement occurred in only 33 per cent of unresponsive patients, usually in association with ancillary treatment, i.e., red cell transfusions, local radiotherapy, and corticosteroids. Without localized radiotherapy, resolution of superficial plasmacytomas after melphalan therapy always was associated with suppression of myeloma globulins to less than 50 per cent of the pretreatment value. Abnormal values for hemoglobin and albumin concentration improved in almost all responding patients, but were ameliorated in a minority of unresponsive patients (Table 1). These differences were significant at the .01 level (Fisher's exact test). Bone marrow plasmacytosis decreased in most responding patients, but the quantitative reproducibility of this parameter was poor even with simultaneous samples from the same subject. Of patients responding in terms of myeloma protein suppression, 13 per cent demonstrated bone recalcification in areas unexposed to local radiotherapy; these changes became apparent 6–24 months after beginning melphalan therapy and were best demonstrated in lateral skull films. The incidence of thrombocytopenia (< 100,000/mm.^{3}), azotemia (BUN > 30 mg.%), and hypercalcemia (> 6.0 mEq/L) was 5, 20, and 21 per cent respectively; the low number of patients with these abnormalities prevented a precise evaluation of the relationship of these parameters to the response to treatment. No relationship was found between objective improvement and age, sex, race, hemoglobin concentration, and serum albumin concentration.

Rate, Degree, and Duration of Remission

Of the 68 patients in whom response was evaluated, urine myeloma globulin excretion exceeded 0.5 Gm. daily in 40, and was the only myeloma pro-

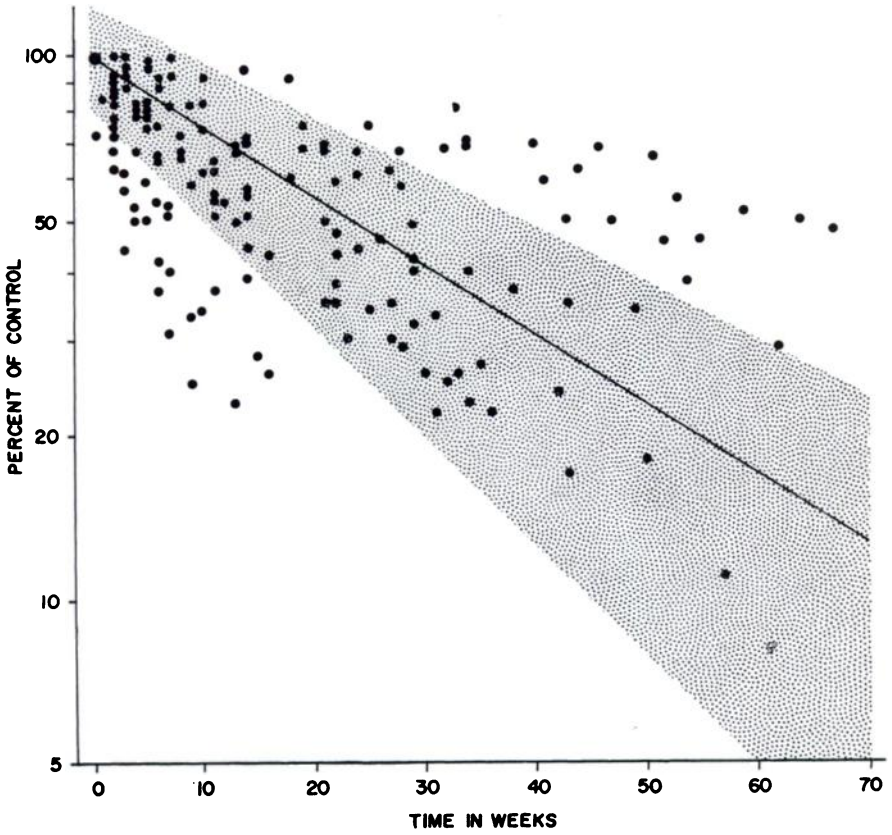


Fig. 1.—Suppression of serum myeloma proteins in responding patients. All measurements, ranging from 3–10/patient, are recorded from melphalan to maximum suppression. A curve was fitted to the data through the control point using the formula, log Y = 4.6–0.03 X. Two-thirds of the values fell within the shaded area.

tein evaluated in 23 patients. The median daily excretion before therapy was 4.3 gm., ranging from 0.8 to 31 gm. A serum myeloma peak was identified in 43 patients, and was the only myeloma protein abnormality in 26 patients. The median concentration was 4.7 gm. per cent, ranging from 1.4 to 11.4 gm. per cent. Both parameters could be evaluated simultaneously in 18 patients. Two additional patients without detectable myeloma globulins were considered evaluable and responsive on the basis of plasmacytoma resolution and skeletal healing.

Urine and serum myeloma globulin decreased to less than 50 per cent of the pretreatment value in 23 of 40 and 27 of 43 patients respectively; in 11 of 18, both parameters fell. After effective chemotherapy, urine myeloma protein decreased more rapidly than serum myeloma protein (Figs. 1 and 2). Of patients responding, 90 per cent had a 25 per cent decrease in the pretreatment value of urine myeloma globulin within 1 month, and of serum myeloma globulin within 3 months.

In responding patients, the myeloma protein decreased to a level which

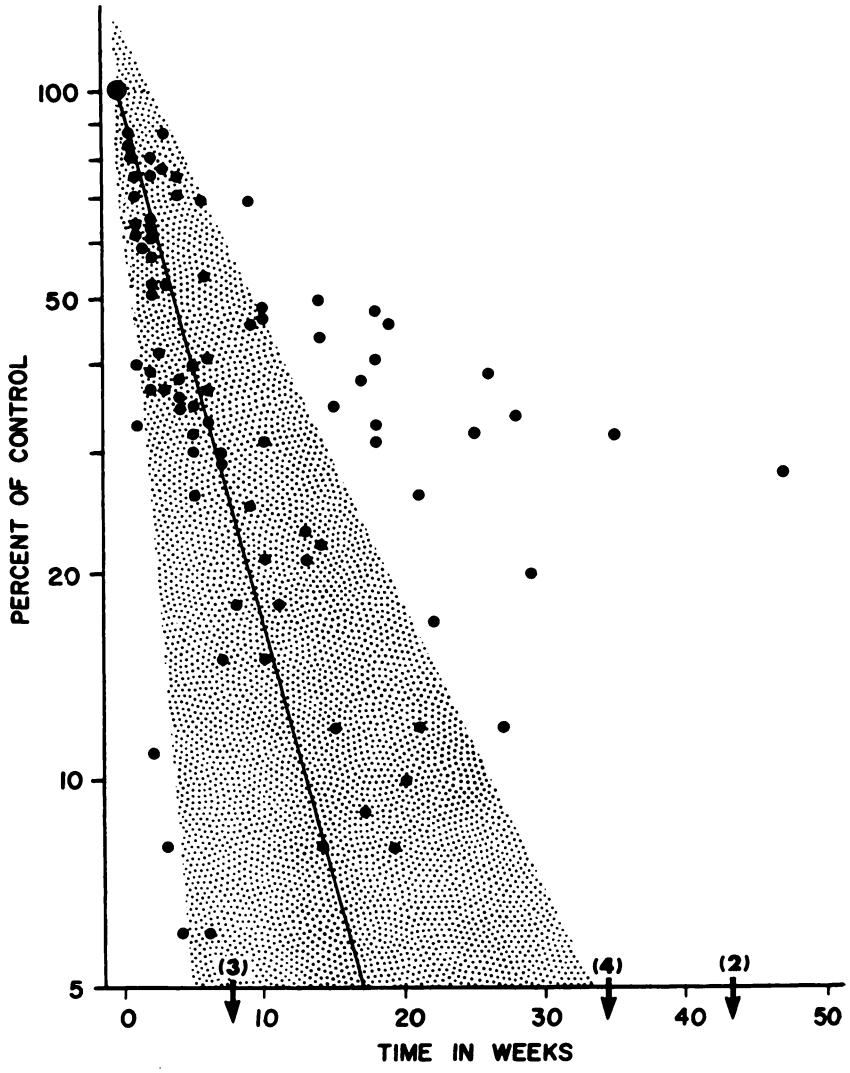


Fig. 2.—Suppression of urine proteins in responding patients. All measurements, ranging from 3–10/patient, are recorded from melphalan to maximum suppression. A curve was fitted to the data using the formula, log Y = 4.6–0.18 X. Two thirds of the values fell within the shaded area.

varied from less than 2 to 49 per cent of the control value. While 24-hour urine protein excretion decreased to less than 150 mg. per day in 10 of 23 responding patients, the myeloma protein peak disappeared from the serum electrophoresis strip in only 4 of 27 patients. However, in no case studied did the abnormal protein disappear when subjected to immunoelectrophoretic analysis. Urine and serum myeloma protein decreased to a median 15 and 34 per cent of the pretreatment value respectively.

Patients usually were free of symptoms related to plasma cell myeloma dur-

Table 2.—*Median Survival in 82 Patients with Plasma Cell Myeloma (Months)*

	No. Dead/Total	From Symptoms	Range	From Diagnosis	Range	From Melphalan	Range
All patients	56/82	42	2-131	34	1-127	23	1-81+
Unresponsive (includes early deaths)*	29/34	18	2-108	15	1-102	9	1-81+
Unresponsive (excludes early deaths)	23/28	23	5-108	17	4-102	11	2-81+
Responsive	20/40	60	5-96+	48	5-70+	41	3-65+

* "Early deaths" consisted of 6 patients who died within 3 months of melphalan. Eight additional patients with incomplete data were not evaluable and their survival data was included only in the life-span calculations for "all patients."

ing periods of sustained regression of myeloma protein; recurrence of symptoms was usually associated with increase in serum and/or urine myeloma globulin levels. By life-table analysis of the interval between decrease in myeloma proteins to less than 50 per cent of control and relapse in a direct manifestation of disease (i.e. myeloma globulins, plasmacytomas, or size and number of lytic bone lesions), the median duration of remission in responding patients was 30 months, ranging from 2 to more than 63 months. The median duration between recognition of relapse and death was 5 months, ranging from 1 to 27 months.

Survival

The median survival time of all 82 patients studied was 42 months from onset of symptoms, 34 months from diagnosis, and 23 months from start of melphalan

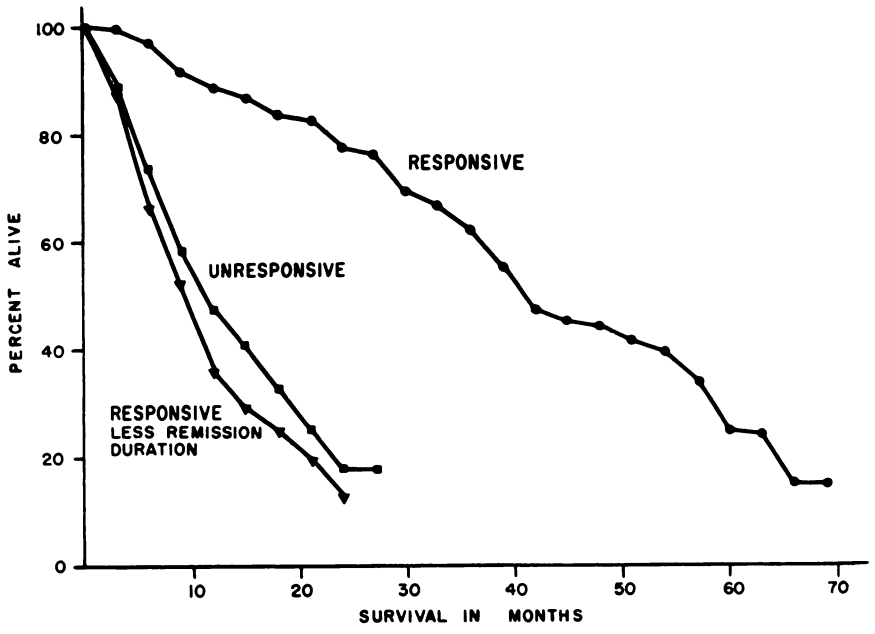


Fig. 3.—Survival from institution of melphalan.

therapy (Table 2). The survival time from beginning melphalan ranged from 3 months ("responding" patient with plasma cell leukemia) to more than 6 years ("unresponsive" patient with stable myelomatosis). Of the 28 unresponsive patients, 5 were alive 3 years following diagnosis. Calculations by the life table method (Fig. 3) indicated that the median survival of patients responsive to melphalan therapy was 30 months longer than the survival of a "comparable" group of unresponsive patients (i.e., excluding early deaths), a difference significant at the .01 level. There was no relationship between survival and age, sex, or race of patients in either responsive or unresponsive groups. Because only 20 responding patients were dead at the time of this report, the relationship between the degree of myeloma protein regression and survival time could not be determined. Prolonged survival occurred more often in unresponsive patients when myeloma protein decreased slightly, or remained stable after melphalan, than in patients with rising myeloma protein levels.

The contribution of remission to the improvement in survival time of responding patients was calculated by subtracting duration of response for each patient from the survival time following melphalan. The resulting median survival, calculated by the life-table technique, was 9 months, a figure similar to that in unresponsive patients (Fig. 3).

Discussion

In a disease with a variety of parameters, such as plasma cell myeloma, the response rate is influenced considerably by the criteria used for evaluation. In this study, only objective effects on direct manifestations of myeloma (e.g., level of myeloma protein relative to pretreatment value) were used to derive a response rate of 49 per cent for all and 59 per cent for evaluable cases. Emphasis on changes in myeloma proteins in evaluating therapeutic response is based upon evidence that these proteins are produced by the malignant plasma cells.[10] Furthermore, animal studies indicate that the amount of myeloma protein correlates directly with the size of plasma cell tumors.[11]

Most patients with substantial decrease in myeloma globulin had improvement in symptomatic status as well as in other disease manifestations, such as anemia and hypoalbuminemia. Unresponsive subjects less often had symptomatic improvement, usually in association with red blood cell transfusions, localized radiotherapy, or corticosteroid therapy for hypercalcemia. The usefulness of marrow differentials in providing an accurate assessment of myeloma activity was limited, an observation consistent with the focal distribution of malignant plasma cells in the marrow.[12] Correction of hypoalbuminemia in most responding patients suggests that a deleterious effect on protein production by melphalan is unlikely, and supports the usefulness of this criterion to confirm clinical response. Conversely, significant regression in myeloma globulin level, in association with persistent or progressive hypoalbuminemia, may not be a valid indication of objective improvement.[13]

Ineffective chemotherapy was usually recognized when stable or increasing levels of urine and serum myeloma protein persisted for more than 1 and 3 months respectively. The more rapid suppression of myeloma globulin in

urine, in comparison with serum, is of interest. Elimination of a substantial proportion of malignant plasma cells should be followed by a decrease in the myeloma protein level at a rate inversely proportional to the survival time of that protein in blood or urine. The observations reported here are thus consistent with studies by Lippincott et al.[14] and Putnam[15] indicating a shorter half-life for Bence Jones protein (less than 24 hours) in contrast to that for serum myeloma protein of γG specificity (6 days). The greater degree of myeloma protein suppression in urine, in contrast to serum, was attributed to the more limited range of myeloma protein change detectable in serum as a result of its higher concentration of normal gamma globulin. Hence, serial measurements of normal and myeloma globulin concentration by the antibody-agar disc diffusion technique[16] before and after chemotherapy may provide a more precise method for assessing the kinetics of response.

The incidence of objective response reported here compares favorably with other large series employing either cyclophosphamide[17] or melphalan[18,19] for plasma cell myeloma. The high response rate of patients in this study was attributed to multiple factors that may have permitted the detection and/or selection of patients with less advanced disease. This impression is based on the assumption that patients referred to a specialized institution with an established diagnosis are less apt to have advanced plasma cell myeloma. Although all patients had symptomatic and multiple bone lesions, the incidence of severe anemia, thrombocytopenia, and uremia was less than in other series.[20] Hence, early deaths occurred in less than 10 per cent of these patients in contrast to 20 per cent of a larger group of patients treated simultaneously in neighboring institutions.[21]

Survival time was prolonged with melphalan therapy, but this effect was limited to a major degree to subjects developing a response in a direct manifestation of disease. Longer life-span may have occurred in a small number of patients with detectable improvement in myeloma globulin level who were unresponsive in terms of the criteria employed. Hence, indefinite treatment with melphalan may lengthen life-span in some unresponsive patients by inhibiting plasma cell proliferation. While median survival time of unresponsive patients was similar to that of patients not treated with alkylating agents,[22] the survival of patients responding to melphalan was prolonged more than 2 years. This observation justifies the criteria employed here for evaluation of response, a conclusion supported by the similar duration of sustained myeloma protein regression and survival prolongation in responding patients.

The similarity in survival time between patients unresponsive to melphalan and responsive patients after subtracting the remission duration indicates that life-span prolongation in responsive patients is accounted for by the duration of objective response; this observation has been described previously only in acute leukemia.[23] Consequently, improved supportive therapy (i.e., transfusions, antibiotics, corticosteroids, etc.) does not prolong survival to a major degree in patients failing to respond to chemotherapy, although such therapy may contribute to the survival of all patients by providing a greater opportunity to respond to melphalan. Therefore, the development of new drugs and

treatment regimens which increase the frequency and duration of objective response offers the best approach to major improvements in the treatment of plasma cell myeloma.

SUMMARY

Of 82 patients with plasma cell myeloma treated with melphalan, 40 (49 per cent) were improved in clinical status and in a direct manifestation of disease. Myeloma protein level provided an important parameter for periodic assessment of disease activity. After effective chemotherapy, myeloma globulins decreased more rapidly and to a greater degree in urine than in serum. Anemia and hypoalbuminemia were improved in most responding patients, thus supporting the usefulness of these parameters in confirming clinical response. Median survival time for all patients was 42 months from symptoms, 34 months from diagnosis, and 23 months from melphalan. The life-span of responding patients was prolonged more than 2 years, a period accounted for by the duration of objective response. Future progress in treatment for plasma cell myeloma will depend more on advances in chemotherapy than upon improvements in supportive care.

SUMMARIO IN INTERLINGUA

Inter 82 patientes con myeloma plasmocytic qui esseva tractate con melphalano, 40 (i.e., 49 pro cento) esseva meliorate in lor statos clinic e in le manifestationes directe del morbo. Le concentrationes de proteina de myeloma provideva un importante parametro pro le evalutation periodic del activitate del morbo. Post efficace chimotherapia, globulina de myeloma declinava plus rapidemente e plus extensemente in le urina que in le sero. Anemia e hypoalbuminemia esseva meliorate in le majoritate del patientes qui respondeva al tractamento. Iste constatation confirma le utilitate del mentionate parametros como indicatores del responsa clinic. Le superviventia median pro le gruppo total esseva 42 menses a partir del prime symptomas, 34 menses a partir del diagnose, e 23 menses a partir del institution del therapia a melphalano. Le superviventia del patientes qui respondeva positivemente esseva prolongate per plus que duo annos. Isto esseva etiam le duration del responsa objective. Le progressos futur in le tractamento de myeloma plasmocytic depende plus de avantiamento in le chimotherapia que de melioration in le mesuras supportative.

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