British Journal of Haematology. **1992. 80.** 55–61

Impact of active and passive exclusions on the results of a clinical trial in multiple myeloma

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Received 10 June **1992:** *nccepcdjor publication 8 September* 1991

Summary. During the 3 years 1984–86, **314** cases of multiple myeloma were diagnosed in the Health Care Region of Western Sweden. 180 of these cases were included in a clinical trial: 71 were notified to the trial but excluded: **49** cases were not reported to the trial; **14** were diagnosed post mortem.

. The crude incidence rate of myeloma was **6.3** cases per 100 000 inhabitants per year. corresponding to an age-adjusted (world standard population) incidence rate of 2.9 cases per 100000 inhabitants per year.

The excluded and the non-reported patients had a significantly shorter survival than those included in the clinical trial (median survival 22. 13 and 33 months, respectively). This was partly due to differences in age and proportion of actively treeated patients between the groups, but the same tendency remained also after correction for these factors.

Considering the included patients separately. the effect of tentative application of presumptive exclusion criteria corresponding to major prognostic factors was studied. Prolonged survival was seen when the upper age limit was lowered and when patients with renal failure or low performance status were excluded.

The results illustrate the fact that for multiple myeloma the survival in a trial population is markedly influenced by active and passive exclusion of patient groups with unfavourable prognostic characteristics. When reporting results of clinical trials. discussion of the representativeness of the trial population for the total patient population is recommended in order to facilitate application of the trial results to medical practice and comparisons between trials.

When results from clinical trials in multiple myeloma are to be transferred to clinical practice one has to consider some facts that make the results difficult to interpret. Treatment results differ considerably between different clinical trials but comparisons are difficult to make because the patient populations often differ from each other with regard to patient characteristics of prognostic importance. e.g. age. stage distribution and performance status. This problem has recently been discussed by Paaske Hansen & Galton (1985) and by Kelly *et al* (1988). Furthermore, hardly any reports on clinical trials discuss the representativeness of the study population in relation to the total population of myeloma patients. In some studies the material contains the majority of myeloma patients with the diagnosis confirmed during the study period, whereas in other studies the material is highly selected due to different active and passive exclusion mechanisms. Knowledge of these factors may be of great importance when results of clinical trials are to be applied in clinical practice.

The purpose of this study is to describe a total population of myeloma patients diagnosed during 3 years within a defined geographical area and to define the relationship between a study material recruited during the same period from the same population for a clinical trial and the total patient population. The total population is analysed and compared with the trial population with respect to prognostic factors and survival. The fate of the non-study patients is described

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and the effect on survival of different plausible exclusion criteria tentatively applied to the trial population is analysed.

MATERIAL

During the period 1 January **1984** to 31 December **1986** a randomized clinical trial on myeloma was performed in Western Sweden (Hjorth *et al.* 1990). Two university hospitals and **16** local hospitals, covering the entire Health Care Region of Western Sweden **(1.65** million inhabitants), co-operated in the study. The participating centres were requested to report all newly diagnosed cases of myeloma, including patients not eligible for the trial. During the study period, a total of 255 patients were reported. **180** patients were included in the trial. 75 were excluded. The reasons for exclusion were high age **(19).** heart disease precluding anthracycline chemotherapy (12). other severe concurrent illness (12). unwillingness to participate (15). renal failure necessitating initial haemodialysis **(4).** non-secreting myeloma (2). plasma cell leukaemia **(1).** multiple myeloma complicated by a large plasmocytoma necessitating irradiation (1). terminal state (1). administrative reasons **(4)** and diagnosis post mortem (4).

In order to find patients not reported to the study. the Regional Swedish Cancer Register was surveyed for all notified cases of myeloma from the same catchment area. diagnosed during the study period. For cases notified to the cancer register but not reported to the study. the medical records were reviewed considering criteria for diagnosis, treatment and survival.

METHODS

Diagnostic criteria. In the clinical trial the following criteria for the diagnosis of multiple myeloma were used: (A) Serum M-protein concentration > 30 g/l (IgG) **or** > 20 g/l (IgA) and, or Bence Jones proteinuria > 1 g/24 h. (B) bone marrow plasma cells > 10%. and (C) osteolytic bone lesions. A diagnosis of multiple myeloma was accepted if criteria A + B or A + C were fulfilled. In the evaluation of patients identified by the survey of the Swedish Cancer Register. in order to include all symptomatic multiple myeloma patients. the somewhat broader Southwest Oncology Group (SWOG) diagnostic criteria (Durie & Salmon. 1977) were used.

Incidence rate *calculation.* To calculate age-standardized incidence rates the 'direct' method was used with the world population as standard (Waterhouse *et al.* **1982).** The age-specific incidence rate was calculated for each 5-year interval.

Treatment regimens. The design of the clinical trial is described in detail elsewhere (Hjorth *et* al. **1990).** Briefly. stage I patients were randomized between traditional intermittent melphalan and prednisone therapy (MP) and initial observation without therapy: when progression occurred, MP was started. Stage II patients were randomized between MP and vincristine. melphalan. cyclophosphamide and prednisone (VMCP) every **4** weeks. and stage III patients between MP and vincristine, carmustine. doxorubicin and prednisone (VBAP) and VMCP alternately every **4** weeks. In the excluded and the non-reported patients. cytostatic therapy, when given, usually consisted of traditional MP therapy.

Table I. Revised diagnoses of **346** cases notified as myeloma to the Swedish Cancer Register

Multiple myeloma. reported to the clinical trial	237
Multiple myeloma. not reported to the clinical trial	59
Other plasma cell disorders	
Solitary plasmocytoma	18
Primary amyloidosis	2
Immunoblastic lymphoma	1
Monoclonal gammopathy of unknown significance	24
No plasma cell disorder	5

Follow-up. All patients were followed up until death or until November **1989.** with a median follow-uptime of 53 months.

Statistical methods. Comparisons between the group of included patients and the other groups were performed using Pitman's test (Bradley. **1968).** When studying the relationship between presumptive prognostic variables. a special survival test was applied in the univariate case (Merck **et** *al.* 1983) and Cox's regression model in the multivariate case. The survival curves were constructed by the life-table method and compared by the log-rank test (Armitage & Berry. **1987).** which is a conventional method when studying the relationship between a zero-one variable and survival. The survival test (Merck *et al.* **1983)** extends the applicability to general variables (e.g. serum calcium) avoiding the idealizing assumptions made by the Cox's model. Two-sided tests were used.

The *effects of plausible exclusion criteria* were calculated as follows: ***For age.*** upper age limits with 3-year intervals from **85** to **65** years were applied to the whole stage II and III patient group and to the included stage II and III patients separately. For each age limit. the median age of the remaining patients was determined and the median survival estimated from the survival curve. Regarding ***renal failure.*** patient groups with serum creatinine values > 500. > **300.** > 200. > 150 and > 120 μmol/l were excluded consecutively and the survival of the remaining patients determined. In a similar manner, patients with a *low performance status.* defined as Karnofsky index ≤ 20% and ≤ 30%. were excluded and the survival of the remaining patients determined.

RESULTS

Survey of the Swedish Cancer Register

During the study period 346 cases of myeloma from the Health Care Region of Western Sweden were notified to the cancer register (Table I). out of which 237 cases were also reported to the clinical trial: **109** cases were not reported to the trial. Out of these, the diagnosis of multiple myeloma according to SWOG criteria was confirmed in **59** cases, **46 of** which also fulfilled the diagnostic criteria of the clinical trial. Ten of these 59 cases were diagnosed post mortem. The diagnoses of the **50** cases that were not considered to be confirmed myeloma in **the present re-evaluation are shown** in Table I.

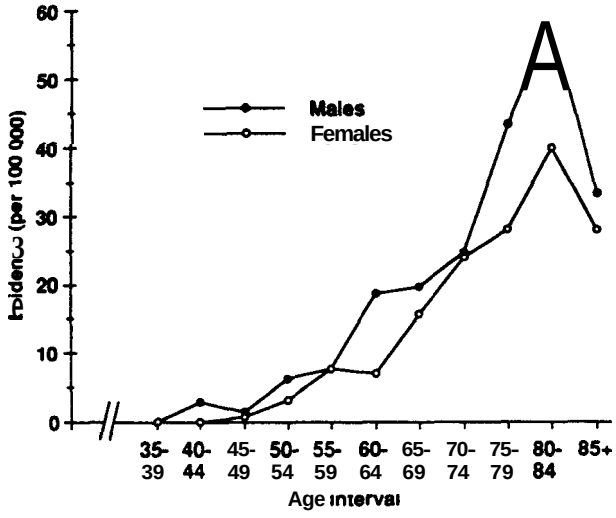

Fig 1. **Age** and sex-specific incidence rates per 100 000 inhabitants per **year** for multiple myeloma in Western Sweden from 1984 to 1986.

Incidence of myeloma

Thus, during the study period of *3* years a total of **314** confirmed cases of multiple myeloma were diagnosed in Western Sweden, with a population comprising 1.65 million Inhabitants. This yields a crude incidence rate of **6.3** cases per 100 000 inhabitants per year, which corresponds to a world age-standardized incidence rate of 2.9 cases per 100000 inhabitants per year. For men. the crude annual incidence rate was **6.8** and the age-standardized incidence rate **3.6** cases per 100000 inhabitants per year. For women. the corresponding figures were 5·9 for crude incidence rate and 2·3 for age-standardized incidence rate. The age-specific Incidence rates increased with age as shown in Fig 1.

Patient groups

The **14** cases of myeloma that were diagnosed post mortem are included in the incidence calculations but omitted from all other analyses in this study. The material used for all analyses except the incidence calculations consists of three groups of patients: **(1) 180** patients reported to and included in the clinical trial. These patients are henceforth referred to as *'included'*. **(2) 71** patients reported to the study but not eligible for the clinical trial. These patients are referred to as *'excluded'*. **(3) 49** patients not reported to the study. These patients are referred to as 'non-reported'.

Patient characteristics

Clinical and laboratory characteristics for the different patient groups are shown in Table II. As expected. age was higher in the excluded group and also in the non-reported group compared to the included group. At age intervals above the median age of the total material. an increasing proportion of patients were excluded from the trial or not reported (Fig 2). Haemoglobin was significantly lower in the non-reported group than in the included group ($P < 0·01$). For other patient characteristics of major prognostic importance—with reservation for the possible omission of some clinically important difference. due to the rather small number of patients—no statistically significant differences were seen between the patient groups.

Fate of the included patients

The results of the randomized trial comparing MP with multidrug chemotherapy for stage II and 111 patients are reported elsewhere (Hjorth et *al*, 1990). In summary. no differences were found in response rate or survival between the treatment arms. Considering the two arms taken together. the response rate as defined by a decrease of the M-protein concentration by >50%. was 63% for stage II patients and **58%** for stage 111 patients. The median survival was 36 months for stage II and 25 months for stage III patients. For stage I patients. randomized between MP and initial observation. interim results have been reported (Hjorth et *al.* **1989).** The median survival is not yet reached: for the two arms taken together. the survival at 48 months is 60%.

Fate of the excluded patients

In this group ($n = 71$) 60 patients (85%) were treated with chemotherapy. usually MP. 28 patients (47%) responded with a decrease of 34-protein by at least 50%. The median survival was 22 months for the whole group (Fig 3) and 26 months for the actively treated patients.

Fate of the non-reported patients

This group was heterogeneous and comprised three categories of patients: **(A)** 11 patients with definite multiple myeloma according to **SWOG** criteria but not fulfilling the formal diagnostic criteria used in the trial. (B) 24 patients that. because of high age ($n = 8$) and/or other coincident illness ($n = 12$) and/or terminal state of myeloma disease ($n = 8$) or other reasons ($n = 2$), presumably were never considered for the clinical trial. and (C) **14** patients that were eligible for the trial but never notified. Out of the whole group. **34** patients **(69%)** were treated with chemotherapy. Considering the three patient categories separately. the number of treated patients was **7/11, 13/24** and **14/14.** respectively. A response. **as** defined above, was noted in **15/34** treated patients **(44%).** The median survival was **13** months for the whole group (Fig **3)** and **17** months for the actively treated patients.

Prognostic factors

Prognostic factors were analysed for the included stage II and III patients only ($n = 149$) (Table III). Univariate analysis showed prognostic importance for age, serum creatinine, haemoglobin, platelet count, serum albumin, corrected serum calcium, performance status and light chain disease. Serum $\beta 2$-microglobulin was not analysed. The multivariate analysis, however, showed independent prognostic importance only for age. serum creatinine. performance status and light chain disease.

Survival

The median survival for the total material was 26 months. Considering the three patient groups separately (Fig **3).** the

Table II. Patient characteristics. Clinical and laboratory Endings in included, excluded and non-reported patients

	Included	Excluded	Not reported	All patients
No. of patients	180	71	49	300
Age				
(median)	69	76	79	72
(range)	41–91	44–90	51–89	41–91
Sex ratio (M/F)	1.1	0·9	1.6	1.1
Stage according to Durie & Salmon				
I	31 (17)†	15 (21)	10 (20)	56 (19)
II	52 (29)	16 (23)	10 (20)	78 (26)
III	97 (54)	40 (56)	29 (59)	166 (55)
Serum creatinine ⩾ 200 μmol/l	33 (18)	13 (18)	7 (14)	53 (18)
Haemoglobin < 85 g/l	23 (13)	12 (17)	9 (19)	44 (15)
Platelet count < 100 × 10^9/l	8 (4)	3 (4)	2 (5)	13 (4)
Serum albumin < 30 g/l	37 (21)	20 (29)	13 (33)	70 (24)
Corrected S-calcium* ⩾ 2.60 mmol/l	68 (38)	25 (36)	18 (44)	111 (38)
M-protein class				
	110 (61)	33 (47)	31 (63)	174 (58)
IgA	37 (21)	22 (31)	6 (12)	66 (22)
IgD	4	0	0	4
IgE, IgM or not analysed	1	1	1	3
Bence Jones only	27 (15)	12 (17)	10 (20)	48 (16)
Non-secreting myeloma	1	2	2	5

* Corrected S-calcium = Serum calcium − 0·02 (Serum albumin − 40).
† Numbers in parentheses are percentages.

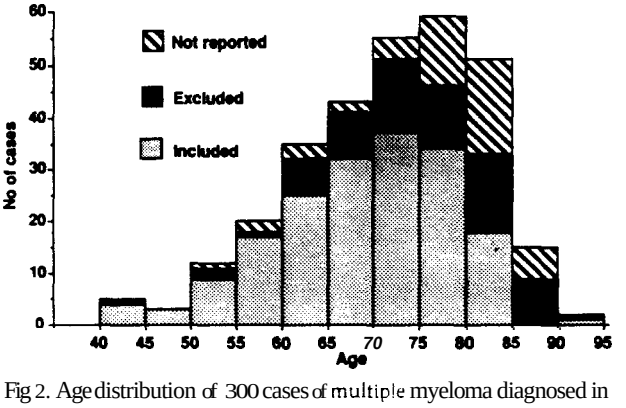

Fig 2. Age distribution of 300 cases of multiple myeloma diagnosed in Western Sweden from 1984 to 1986. Included = Included in the clinical trial ($n = 180$). Excluded = Notified but excluded from the clinical trial ($n = 71$). Non-reported = Sot reported to the clinical trial ($n = 49$).

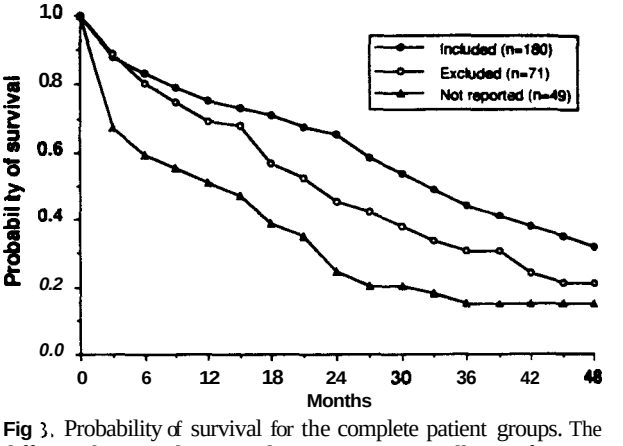

Fig 3. Probability of survival for the complete patient groups. The difference between the survival curves was statistically significant for included versus excluded ($P < 0·05$), included versus non-reported ($P < 0·001$) and excluded versus non-reported patients ($P < 0·05$).

median survival was 33 months for the included. 22 months for the excluded and 13 months for the non-reported group. The differences between the three survival curves were statistically significant ($P < 0·05$). After correction for the age differences between the patient groups. there was still a significant difference between the included and the non-reported patients. When a similar comparison was restricted to patients treated with chemotherapy. there was still found a significant difference between the survival curves for included and non-reported patients. also after correction for age ($P < 0·05$).

Survival and its dependence on age

To study the dependence of survival on age distribution, the patient material was reduced by tentative application of a series of upper age limits with 3-year intervals from 85 to 65 years (Fig 4). Considering the included stage II and III patients first. the number of remaining patients was now consecutively reduced from 149 to 61 and there was a concomitant progressive decrease of the median age of the remaining patients from 68 to 60 years. The effect on survival was a corresponding prolongation of median survival from 30 to 35 months.

Table III. The prognostic effect of some variables estimated by multivariate Cox analysis

Variable	Mean ± SD	Death risk ratio for increase of the variable by 1 SD	Confidence interval for death risk ratio
Age (years)	67·8 ± 9·4	1·36	1·08–1·70
Serum creatinine (μmol/l)	175 ± 182	1·41	1·23–1·63
Haemoglobin (g/l)	106 ± 21	1·03	0·84–1·27
Platelet count (x 10⁹ l)	241 ± 97	0·85	0·69–1·05
Serum albumin (g l)	34·2 ± 6·3	0·83	0·66–1·04
Performance status* (%)	63 ± 25	0·67	0·54–0·83
Light chain disease†		2·13†	1·05–4·30

* Karnofsky index.

† For light chain disease death risk ratio was calculated for the 27 patients with only Bence Jones proteinuria versus the 153 patients with other Ig classes.

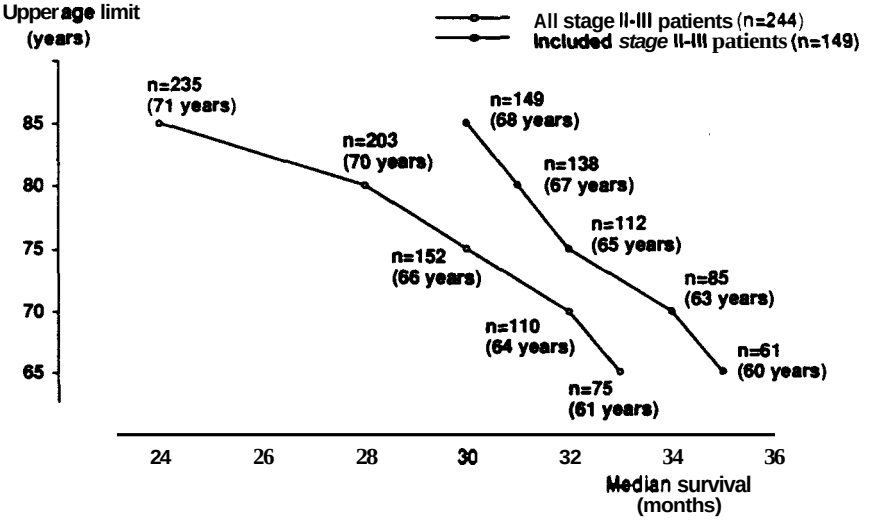

Fig 4. Effect on survival of different upper age limits in a population of multiple myeloma patients. The median age of the remaining patients in each group is given in parentheses.

Table IV. Effect on survival of the exclusion of patients with renal failure

upper limit for serum creatinine (μmol/l)	No. of patients	Median survival (months)
No limit	149	30
500	139	31
300	131	32
200	116	33
150	106	34
120	87	36

Secondly, for the sake of comparison. a similar calculation as made for all stage II and III patients ($n = 244$). For the whole of this group without any upper age limit. the median age was 72 years and the median survival 24 months. When the group was reduced by application of upper age limits decreasing from 85 to 65 years, the number of patients was successively reduced to 75 with a concomitant lowering of the median age of remaining patients to 61 years and a corresponding prolongation of median survival to 33 months (Fig 4).

Table V. Effect on survival of the exclusion of patients with low performance status

Exclusion of patients with Karnofsky index	No. of patients	Median survival (months)
—	149	30
⩽20%	140	31
⩽30%	122	33

Survival and its dependence on exclusion of patients with renal failure

In a similar manner. the effect on survival for the included stage II and III patients was studied by applying different upper limits for serum creatinine. As a result. the median survival in the material was substantially prolonged when patients with high serum creatinine values were excluded (Table IV). For instance. if patients with serum creatinine values >200 μmol/l ($n=33$) were excluded the median survival was prolonged from 30 to 33 months.

Survival *and its dependence on performance status*

The exclusion of patients with low performance status was shown to bring about a similar effect on survival (Table V). For instance. if patients with a Karnofsky index $\leqslant 30\%$ were excluded from the analysis. the median survival was prolonged from 30 to 33 months.

DISCUSSION

Multiple myeloma is a disease which primarily affects older patients. In Sweden. the crude incidence of multiple myeloma is high compared to many other countries because of a high and steadily increasing proportion of old patients in the population. But the age-adjusted incidence rate is also high compared to other recent reports (Linos *et al.* 1981: Turesson *et al.* 1984; Shapira & Carter. 1986; Nandakumar *et al.* 1988; Karjalainen & Palva. 1989; Hansen *et al.* 1989; Carli *et al.* 19891. The high incidence tigures in this study do not necessarily reflect a higher real incidence than in other countries but rather a high diagnostic intensity combined with a high notitication rate. resulting from the requirement of notitication of all newly diagnosed cases both to the ongoing clinical trial and to the Swedish Cancer Register.

The Swedish Cancer Register is based on the notification duty for both clinicians and pathology cytology laboratories concerning all newly diagnosed malignant and certain benign tumours. The reliability of the Kegister has been evaluated by Mattsson (1984). who. by comparison of the notitications in the Cancer Register during 1978 with cancer diagnoses notitied to the Cause-of-Death Register and the In-Patient-Care Register of Stockholm County. found a registration deticit for multiple myeloma of 5·8% for Stockholm County and 16·3% for the whole of Sweden. In the present study we found a registration deticit in the Cancer Register of 4·5%. On the other hand. the review of the medical records of patients notitied to the Cancer Kegister but not to the trial revealed an over-notification in the Cancer Register by 16%. partly due to co-registration of other malignant plasma cell disorders. mostly solitary plasmocytomas. partly to incorrect notitication of nonmalignant plasma cell disorders. mostly MGUS. Thus, according to this study, the figures of the Cancer Register give in an overestimation of the real incidence of multiple myeloma by about 10%.

Prognostic factors in multiple myeloma have been analysed and reported from several studies. Recent reviews have been published by Paaske Hansen & Calton (1985) and Kelly *et al* (1988). In the present study. old age. impaired renal function. performance status and light chain disease were found to have independent negative effects on survival. Among prognostic factors. high age. renal failure and low performance status constitute patient characteristics that are liable to cause passive exclusions from a clinical trial. with a potential corresponding impact on the results of the trial (see below).

When the results from a clinical trial are to be applied in clinical practice. it is necessary to know whether the studied patient population is representative of the majority of patients with the disease or not. In a disease like multiple myeloma, with a steeply increasing age-related incidence. this point has special significance because clinical trials are mostly carried out on patients of considerably lower ages than the majority of patients in clinical practice. This issue is addressed by Cohen & Bartolucci (1985). who. based upon experiences from a clinical trial performed in 1972–76 by the Southeastern Cancer Study Group. concluded that older patients had the same responses and survival rates as younger patients. In that study. 21% of the patients were $\geqslant 70$ years. compared to 47% projected for the total multiple myeloma patient population. The corresponding figures for the present study are 50% and 61%.

In the present study. the matter of representativeness is illustrated in two ways. Firstly. the population of patients that were not included in the clinical trial was identified and studied regarding prognostic factors. treatment and survival. Secondly. the impact on survival of excluding patient groups with poor prognostic characteristics from the trial material was analysed.

In this study. 60% of all cases diagnosed ante mortem were included in the clinical trial. Out of the remaining patients. 24% were actively excluded from the trial. 16% were never reported to the trial and thus passively excluded. The majority of these patients. if notitied. would also have been actively excluded from the trial because of high age and other coincident diseases and at most 5% of the total patient population could possibly have been added to the trial. Thus. the representatives of this trial population was limited to patients that were under the age of 85 years and free from other severe diseases.

The effect of other exclusion criteria on the results of the trial is illustrated by the calculations of survival after the application of different plausible exclusion criteria to the trial material. The results show that the exclusion of higher age groups. patients with renal failure and patients with low performance status has a considerable effect on the survival figures. in a clinical trial. exclusion of patients with these characteristics may be active. according to the exclusion criteria in the study protocol. or passive. because of referral patterns and participating clinicians' hesitance to consider certain categories of patients for randomized trials. Publications on clinical trials seldom contain information regarding these exclusion possibilities.

A management trial. trying as far as possible to imitate day-to-day clinical practice. should ideally include a study population that mirrors the total patient population. This can be achieved by including all cases in a given population or by including a randomly selected group of patients. In haematology, the latter is generally not feasible because of insufficient

number of available cases. Therefore. when management trials are planned. every effort should be made to include as many actively treatable patients as possible out of the given population. But even with a masimal effort. a considerable proportion of patients will not be included in the trial. Knowledge of the differences between included and non-included patients is important—not for the interpretation of the results of a comparison between treatment arms in a randomized study. but when the results of the trial are to be applied to the whole patient population and when comparisons with other trials are made.

In conclusion. this study illustrates how the survival of a study patient population is influenced by the inclusion and/or exclusion of patient groups with unfavourable prognostic characteristics. When the results of a clinical trial is to be transferred to clinical practice it is necessary to know how the patient population of the trial has been selected from the totai patient population. When a clinical trial is reported. a discussion regarding the representativeness of the study Population is recommended.

ACKNOWLEDGMENTS

We wish to express our gratitude to Anders Oden for statistical advice. Susanne Amsler-Nordin for secretarial assistance, and the members of the Myeloma Group of Western Sweden for rewarding collaboration.

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