Melphalan and Prednisone (MP) versus Vincristine, BCNU, Adriamycin, Melphalan and Dexamethasone (VBAMDex) Therapy for Multiple Myeloma

Early Results of a Multicenter Trial

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Key Words

Multiple myeloma
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Summary

136 untreated multiple myeloma patients of stage II and III were collected in the study. 37/51 stage II patients had progressive disease and were treated with melphalan and prednisone (MP). 85 patients were of stage III and randomized into MP and vincristine, BCNU, adriamycin, melphalan and dexamethasone (VBAMDex) treatment groups. 55% of MP treated patients responded versus 75% of the VBAMDex group. Since the study has been activated only 16 months ago, no difference in survival could be observed.

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Schlüsselwörter

Multiples Myelom

Induktionstherapie

Zusammenfassung

136 unbehandelte Patienten mit multiplem Myelom der Stadien II oder III wurden bisher in die Studie aufgenommen. 37/51 Patienten im Stadium II mit nachgewiesenem Tumorprogreß wurden mit MP behandelt. 85 Patienten im Stadium III erhielten randomisiert Melphalan und Prednison (MP) oder Vincristin, BCNU, Adriamycin, Melphalan und Dexamethason (VBAMDex) Chemotherapie. 55% der mit MP und 75% der mit VBAMDex behandelten Patienten sprachen auf die Behandlung an. Nach kurzer Studiendauer (16 Monate) konnte zwischen beiden Therapiearmen bisher kein Unterschied in der Überlebenswahrscheinlichkeit festgestellt werden.

Introduction

Since the introduction of chemotherapy with melphalan and prednisone (MP) for multiple myeloma two decades ago [1], no other drug combination has been convincingly shown to induce a better survival despite increased remission rates with several different schedules [2, 3]. In a phase II study we have found that the multidrug combination vincristine, BCNU, adriamycin, melphalan, dexamethasone (VBAMDex) could induce considerably higher remission rates with acceptable toxicity than expected for MP both in untreated and in pre-treated myeloma patients [4]. Therefore, we have initiated a phase III multicenter trial to test VBAMDex versus MP induction therapy in stage III myeloma patients. Here we present early results. Other questions to be investigated in this trial include the efficacy of intravenous MP treatment in stage II patients, the timing of chemotherapy in stage II, the clinical application of in vitro cytostatic drug testing, the evaluation of new prognostic criteria, and whether stage II and III patients after successful remission induction benefit from α -interferon maintenance therapy. At present, the still short observation time only allows preliminary answers to some of these questions.

Patients and Methods

During 16 months since May 1988, 136 untreated stage II and III myeloma patients (Durie and Salmon classification [5]; tab. 1) were

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collected by 25 hospitals. 14 stage II patients had stable disease at the time of diagnosis and are carefully followed without any treatment, whereas 37 stage II patients had initially, or developed progressive disease. The latter group received MP chemotherapy. 85 stage III patients were randomized to receive either MP or VBAMDex induction therapy. The chemotherapy cycles were repeated until no further tumor cell mass (TCM) reduction [6] or clinical improvement occurred, and were discontinued if a significant tumor progression was observed. A response was defined as more than 25 % TCM reduction, a progression as more than 25% increase of the TCM. The response of patients without measurable serum myeloma protein was assessed by objective

Kidney failure Bleeding Hyperviscosity Other tumor related Tumor unrelated
in some patients several

clinical parameters, e.g. enlargement of bone lesions, changes in bone marrow infiltration, quantity of Bence-Jones proteinuria, or hypercalcemia.

Chemotherapy schedules:

MP: melphalan 15 mg/m² i.v. day 1; prednisone 60mg/m² p.o. days 1–4; q 4 weeks.

VBAMDex: vincristine 1 mg/m², adriamycin 15 mg/m², and melphalan 7 mg/m² i.v. days 1, 15, 29, 43; BCNU 40 mg/m² i.v. day 1; dexamethasone 25 mg/m² i.v. days 1–4, 15–18, 29–32, 43–46.

Results

14/51 stage II myeloma patients have a stable disease and are at present not on chemotherapy (tab. 1). They have been followed for between 81 and 480 days. 5/51 patients developed after 48–332 days observation aggressive disease and then received MP treatment, as well as 32/51 patients who presented initially a progressive tumor. 16 stage II patients are evaluable for response. 50% achieved a remission, whereas in 25 % a stable and in 25 % a progressive tumor was observed (tab. 2).

The efficacy of the induction therapies of 40 stage III patients has been analyzed at the present time. The response rates were 55% in the MP arm versus 75% in the VBAMDex treated patient group (tab. 2).

2 stage II and 14 stage III patients died (tab. 3). The analysis of these patients data showed no significant differences concerning treatment related deaths in both, the MP and the VBAMDex treatment arms. In addition, there was no difference in survival probability. However, the median observation time of 201 days is still very limited.

Discussion

It has been generally accepted that stage I myeloma patients should not be treated with chemotherapy. In contrast, stage II patients usually have been put on therapy immediately after diagnosis [3]. The data of our present study show that a considerable number of stage II patients obviously present a long lasting stable disease at the time of diagnosis and should not receive chemotherapy at once. This result, if corroborated by further long time observation, will be of principle importance for treatment strategies in multiple myeloma. The response rate of 55 % for MP treated stage III patients is similar to results of an earlier trial with oral melphalan [3]. 75% response in VBAMDex treated stage III patient is in accordance with previous experience in an uncontrolled study [4], so that with increasing numbers of patients a significantly higher response rate is to be expected in VBAMDex patients. At the present time it is too early to draw any conclusions concerning survival in both stage III treatment arms. Toxicity necessitating discontinuation on the treatment modalities has not been observed so far.

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