Therapy studies in multiple myeloma.

Dobbenburgh, Otto Arij van

Summary

Chapter 1 consists of a review of the literature in which the following aspects of multiple myeloma are discussed:

a) history
b) differential diagnosis of a monoclonal immunoglobulin
c) symptomatology
d) criteria for the diagnosis
e) staging of the disease
f) treatment
g) prognosis
h) cytokinetic data

The background and the purpose of this thesis: the improvement of the management of this disease by the use of the new drug vindesine, are discussed.

In Chapter 2 an investigation into the benefits and toxicity of a treatment regimen consisting of vindesine and prednisone is described. Vindesine (desacetyl-vinblastine amide sulphate, Eldisine®) is a vinca alkaloid differing from the two earlier drugs vincristine and vinblastine. It was used in this phase-II trial because it has less neurotoxic potential than vincristine. The regimen was applied in 40 patients with multiple myeloma resistant to melphalan-prednisone. Thirty-four of these patients could be evaluated. Five patients showed a 'partial response' (more than 75% reduction of m-protein level) and four showed an 'improvement' (more than 50% reduction). Eighteen patients showed a m-protein reduction between 0 and 50% and in seven patients disease progression occurred without reaction to therapy.

Treatment was continued in the nine responding patients. The initial response was short-lasting: four patients showed progressive disease after 14 to 30 weeks. Three patients died of infection, while no signs of renewed tumour activity were present. One patient died of an unknown cause and only one patient is in long term remission. Other side effects were alopecia (15% of the patients) and fingertip paraes-

thesias (50% of the patients). Leukopenia was infrequently observed and never severe.

These results indicate a potential therapeutic effect of vindesine at least in some cases of multiple myeloma. However, the combination with prednisone as used in the present study does not seem promising. Additional investigation of the effects of vindesine – with or without other drugs – seems necessary before a definitive evaluation of vindesine in this disease can be made.

Chapter 3 presents the results of an investigation into the effectivity and toxicity of a new combination therapy for patients with melphalan-resistant multiple myeloma.

This regimen – based on the foregoing observations on vindesine – consisted of cyclophosphamide 500 mg/ m^2 intravenously on day 1 (or orally divided over day 1-5), adriamycin 25 mg/ m^2 intravenously on day 1, prednisone 60 mg/ m^2 orally on day 1-5 and vindesine (Eldisine®) 2 mg/ m^2 intravenously on day 1. The regimen ('CAPE') was administered every three to four weeks.

Nine of the twenty patients that could be evaluated had been treated with other second-line regimens before they received CAPE. The response criteria were the same as in Chapter 2. Two 'partial responses' and two 'improvements' were observed. Eleven patients showed 'stable disease' while in five patients tumour progression continued. Median survival calculated from the start of CAPE was thirteen months. At the moment of evaluation fourteen of 22 patients were alive.

Adverse effects were nausea, vomiting and alopecia in the majority of the patients. In two patients congestive heart failure developed, which may have been induced by adriamycin (cumulative doses of 560 and 300 mg/ m^2 in these patients). Bone marrow toxicity resulted in mild to severe leukopenia in eleven patients and in moderate to severe trombocytopenia in three patients. Two patients died while they were leukopenic; both were already leukopenic before CAPE was started.

The management of patients with melphalan-resistant multiple myeloma is cumbersome and rarely satisfactory. These patients frequently have bone marrow insufficiency due to previous chemotherapy and/or replacement by plasma cells. At present there is no generally accepted treatment (see also Chapter 1). Further use of CAPE in a larger patient population seems appropriate so that the indication for this or a similar combination can be established.

In Chapter 4 the value of β2-microglobulin (β2-m) determinations in serum in the management of patients with multiple myeloma is

investigated. In a retrospective analysis of 87 patients it was shown that serum β2-m levels at the time of diagnosis did not correlate with the disease stages of Durie and Salmon. β2-m serum levels also did not discriminate between patients with MGUS (n = 85) and patients with multiple myeloma stage 1A.

Initial β2-m levels correlated significantly with haemoglobin levels, serum calcium levels, the IgG levels in IgG myeloma, the TBMC (calculated tumour cell mass), the Karnofsky Performance Score and serum creatinine levels. The r-values for these correlations where low, except for the correlation with creatinine (r = 0.68). After correction for renal function (β2-m M/CTD) correlation remained significant only for haemoglobin and IgG levels. The r-values were low.

For survival a significant correlation with the initial β2-m serum level was found. Patients with an initial β2-m below 2.9 μg/ml lived longer than patients with a β2-m level above 2.9 μg/ml (respective median survival times were 65 and 25 months). In a multivariate analysis with renal function, age, TBMC, serum calcium, haemoglobin level and β2-m only the serum creatinine, the TBMC and the age had independent prognostic value. From data in the literature it is known that serum β2-m levels are strongly influenced by the kidney. Thus, the prognostic value of β2-m reflects that of the renal function.

The relation between changes in β2-m levels and changes in TBMC after six or twelve months of treatment was investigated. No correlation between these parameters was found. It is concluded that β2-m levels correlate only minimally with the tumour mass while they do not have additional value for the prediction of the prognosis.

Chapter 5 contains the results of a pilot study in which 6 patients with multiple myeloma stage IIIA (high tumour load) were treated with an experimental chemotherapy combination. This combination had been designed on the basis of cytokinetic data from the literature. The regimen consisted of cyclophosphamide 500 mg/m^2 and methylprednisolon 600 mg/m^2 on day 1 followed by vindesine 2 mg/m^2 on day 8.

Two patients showed a rapid response and remained in remission although one of them died with a paraplegia due to an intraspinal growing plasmacell mass. Two patients showed a gradual response and remained in remission in excellent condition. Finally, two patients showed a rapid response followed by a rapid return of tumour activity.

Thus, the rapid return of disease activity which had previously been reported in 'rapid responders', could not be prevented. Since this was the goal of this drug combination, no further patients were treated. The toxicity was minimal, allowing a dose escalation, which can probably result in a more effective regimen.

The possibility of testing drug sensitivity of the tumour in vivo was discussed in Chapter 6. In eighteen patients with melphalan-resistant multiple myeloma spermidine levels have been measured by radioimmunoassay, before and after an intravenous vindesine administration. The patients were then treated with the vindesine-prednisone combination described in Chapter 2. Afterwards the clinical response was compared with the rise of the spermidine plasma level. Six patients showed a tumour reduction and in five of them a significant rise of the plasma spermidine level had occurred after the vindesine injection.

In ten out of eleven non-responders no spermidine rise was measured. Base line plasma spermidine levels did not discriminate between controls and patients and also not between responsers and non-responders.

The significant correlation between a rise in plasma spermidine level and a therapeutic response point to the feasibility of tumour-drug sensitivity testing in vivo. This study concerned only patients with melphalan-resistant myeloma. Additional studies in patients with other malignant diseases should be performed to see whether this method is useful for treatment selection individual patients.