Cancer Chemother Pharmacol (1994) 34: 356–360

Cancer Chemotherapy and Pharmacology

Clinical trial report

Bi-weekly vincristine, epirubicin and methylprednisolone in alkylator-refractory multiple myeloma

Mark Vincent[1], Glen Goss[2], Clive Sinoff[3], Colin Germond[3], Tom Bozek[4], Gilles Helie[5], Terry Koski[3], Sue Corringham[6], Robert Corringham[6]

[1] London Regional Cancer Centre, 790 Commissioners Road East, London, Canada
[2] Ottawa Regional Cancer Centre, General Devision, 501 Smyth Road, Ottawa, Canada
[3] Northeastern Ontario Regional Cancer Centre, 41 Ramsey Lake Road, Sudbury, Canada
[4] Guys Hospital, London, England
[5] Laurentian Hospital, Sudbury, Canada
[6] School of Medicine, University of California, San Diego, Calif., USA

Received: 22 July 1993/Accepted: 9 February 1994

Abstract. Nine patients with poor-prognosis, alkylator-refractory stage III multiple myeloma (MM) were treated with a 23-h continuous infusion (CI) of a compatible mixture of vincristine (VCR) and epirubicin (EPI) daily for 4 days along with a daily 1-h infusion of high-dose methyl prednisolone (MP) to total of 5 days (VEMP); cycles were repeated every 2 weeks when possible, usually on an outpatient basis. WHO grade 3 or 4 neutropenia and infection were the predominant toxicities encountered, necessitating some treatment delays and dose reductions. Two patients died during treatment. Peripheral neuropathy necessitated discontinuation of the VCR in six patients without obvious loss of efficacy of the regimen. Skeletal muscle dysfunction and cardiomyopathy did not occur; trivial ECG abnormalities occurred during a minority of infusions but were of indeterminate relationship to the chemotherapy. Confusion occurred in two patients; alopecia was frequent but reversible, and mild/moderate dyspepsia and stomatitis were common but easily managed. Eight patients achieved a partial response (PR); another patient experienced early death during his second cycle before response assessment. The median survival from the first VEMP administration was 9 months (range, 1–64 + months), the median response duration was 7 months (range, 1–64 + months). Two patients experienced responses too short to be clinically relevant (≤2 months). An analysis of weekly paraprotein estimations suggests that the intended bi-weekly cycle length may be optimal. Six of these nine patients derived major benefit from this bi-weekly regimen, which deserves further exploration.

Key words: Vincristine – VEMP – Myeloma – Bi-weekly

Introduction

Alkylator-based salvage regimens are relatively ineffective in patients with multiple myeloma (MM) who fail standard alkylator-induction regimens [4]. A popular alternative for these patients (VAD) consists of a 4-day continuous infusion (CI) of VCR and doxorubicin, repeated every 28 days, with intermittent high doses of oral dexamethasone [3]. VAD is more likely to work in initially responsive than in initially refractory patients [65% vs 32% partial remission (PR) rate] [2]. A similar regimen (VAMP) substitutes MP for dexamethasone because of a lesser likelihood of skeletal myopathy; furthermore, this regimen is given on a 3-weekly basis. In refractory myeloma, a response rate of 36%, a median duration of remission of 11 months and a median survival of 20 months have been reported [7]. This type of salvage regimen might be optimized by shortening the cycle length as a means towards dose intensification, since the myelosuppression thus far reported for the VAD and VAMP regimens has been mild [3, 7].

EPI is an analogue of doxorubicin with less cardiotoxicity [11, 13, 15]. Given the typical age of MM patients and the need to limit cardiotoxicity over the frequent, multiple treatments envisaged, EPI was our preferred anthracycline. Originally we had no direct evidence of the efficacy of EPI in MM, but EPI and doxorubicin generally share a similar spectrum of activity [6]. Subsequently EPI was shown to achieve a single-agent response rate in 1/14 alkylator-refractory patients [5] approximating the 1/9 response rate reported for single-agent doxorubicin in similar patients [1]. Our intention was to escalate the EPI dose from 12 mg/m^2 per day (thought to be equimyelosuppressive with the doxorubicin dose of 9 mg/m^2 per day in the VAD and VAMP regimens) to the maximally tolerated dose (MTD) for each patient.

Abbreviations: VEMP, Vincristine, epirubicin and methylprednisolone; MM, multiple myeloma; PR, partial response; VAMP, vincristine, Adriamycin and methylprednisolone; CR, complete response; PD, progressive disease; MTD, maximally tolerated dose; VCR, vincristine; EPI, epirubicin; LVEF, left ventricular ejection fraction as determined by multiple ECG-gated radionuclide cineangiocardiography; MP, methylprednisone

Correspondence to: Dr. Mark Vincent, Medical Oncology, London Regional Cancer Centre, 790 Commissioners Road East, London, Ontario N6A 4L6, Canada

Table 1. Patient's characteristics and outcome

Unique number	Alkylators: primarily or secondarily refractory	Previous exposure(s) (months)	Type	Number of VEMP cycles	Current status and survival (months)	Cycles delayed: on time[a]	MTD of epirubicin × 4d q2/52	Vincristine	Response (duration in months)	Reasons to stop VEMP
1.	Primarily	Melphalan (4) Cyclophos (3)	IgG lamda	20	Alive in plateau phase (64 +)	5:14	6 mg/m² per day	Stopped after 1 cycle	PR (64 +)	Plateau phase
2.	Secondarily	Melphalan (14)	IgG kappa	6	Dead, off Rx, myocardial infarction (29)	3:2	6 mg/m² per day	Stopped after 5 cycles	PR (5)	Toxicity and in plateau phase
3.	Secondarily	Melphalan (10) Cyclophos (47)	Bence-Jones only, kappa	5	Dead, PD, off Rx (10)	2:2	12 mg/m² per day	Not stopped	PR (7)	Toxicity and in plateau phase
4.	Primarily	Melphalan (1) Cyclophos (4)	IgG lamda	2	Died during 2nd cycle (1)	1:0	9 mg/m² per day (?)	Not stopped	Paraprotein halved; time insufficient	Sudden death during Rx
5.	Secondarily	Melphalan (24)	IgA lamda	5	Died, PD, off Rx (5)	0:4	3 mg/m² per day	Stopped after 1 cycle	PR (1)	Toxicity (confusion during 5th cycle), in plateau phase
6.	Primarily	Cyclophos (1)	IgA (? sub-type)	5	Died, ? cause after cycle 5 (3)	1:3	12 mg/m² per day	Not stopped	PR (3)	Unexpected death during Rx
7.	Primarily	Melphalan (3)	IgA kappa	12	Died, off Rx, PD (26)	3:8	6 mg/m² per day	Stopped after 4 cycles	PR (8)	Plateau phase
8.	Secondarily	Melphalan (15) Cyclophos (2)	IgG kappa	6	Died, PD, off Rx (9)	2:3	6 mg/m² per day	Stopped after 2 cycles	PR (4)	Toxicity
9.	Secondarily	Cyclophos (14)	IgG kappa	8	Died, PD, off Rx (8)	5:2	6 mg/m² per day	Not stopped	PR (7)	Plateau phase

Cyclophos, Cyclophosphamide; PD, progressive disease; Ig, immunoglobulin; Rx, treatment; PR, partial remission
[a] The last cycle has to be excluded from this computation, as the cycle-length concept is not applicable

Single-agent VCR has been reported to be quite ineffective in refractory MM [10], but VCR together with high-dose MP given bi-weekly has achieved a PR of 31% and disease stabilization in 25% of 16 patients with refractory MM [8]. We included VCR because of its traditional association with doxorubicin and steroids in this context.

High doses of corticosteroids given as single agents result in remissions in about 40% of both primarily and secondarily refractory MM [4]. For this reason, as well as the non-myelosuppressive nature of these agents, we chose to include a corticosteroid in our dose-intensified regimen but preferred MP over dexamethasone for the reason stated above.

Our major objectives were to assess the feasibility of a bi-weekly VEMP regimen and to discover the MTD of EPI (in combination) in these alkylator-refractory MM patients with diminished marrow reserve; in addition, we wished to determine whether the efficacy would warrant further exploration of this regimen. Furthermore, by measuring weekly paraprotein levels, we wished to assess how frequently an undesirable rise would occur when bi-weekly cycles were given as intended, as opposed to those cycles that might have to be delayed because of myelosuppression (which would therefore resemble the traditional 3- to 4-week cycle length).

Patients and methods

Nine alkylator-refractory patients with confirmed MM were enrolled between May 1987 and March 1990 (Table 1). Three patients were primarily refractory and six were secondarily refractory, i.e. they had responded initially but upon suffering a relapse had failed to respond again to rechallenge with a conventional alkylator/prednisone regimen. Three patients had received only melphalan and prednisone; two, only cyclophosphamide and prednisone; and the remaining four, both melphalan and cyclophosphamide. No patient had had prior exposure to anthracyclines, VCR or high-dose steroids. Seven patients were men, and the median age was 62 years (range, 50–79 years). All patients had stage III disease; five had IgG paraproteins (three, sub-type kappa; two, sub-type lambda), three had IgA paraproteins (one, sub-type kappa; one, sub-type lambda; one, sub-type unknown) and one patient produced only kappa Bence-Jones protein (BJP). One patient had a WHO performance status (PS) of 0, five had a PS of 2 and three had a PS of 3. Excluded were patients with a history of documented peptic ulcer, currently unstable diabetes mellitus, a left ventricular ejection fraction (LVEF) of $<45\%$, uncontrolled infection or coexisting malignant disease. Renal failure was not an exclusion criterion.

Patients gave informed consent and the study was approved by the Ethics Committee of the Laurentian Hospital, Sudbury, Ontario. Treatment was given via a central line (in patients only) or, preferably in ambulatory patients, via a Port-a-cath or Hickman line. MP (1 g/m²) was given each day as a 1-h infusion and was also given at the end of

Table 2. Toxicities encountered

	WHO grade				
	0	1	2	3	4
Granulocytopenia	0	0	2	3	4
Thrombocytopenia	4	1	3	1	0
Infection	0	1	1	5	2
Peripheral neuropathy	3	4	2	0	0
Confusion	7	0	1	1	0
Stomatitis	3	3	2	1	0
Diarrhoea	6	3	0	0	0
Constipation	1	6	1	1	0
Nausea/vomiting	4	1	4	0	0
Alopecia	2	4	3	0	0
Cardiac rhythm[b]	5	4[a]	0	0	0
Cardiac function	9	0	0	0	0
	Other scales				
Skeletal myopathy[c]	5/5:7	4/5:2	3/5:0	2/5:0	1/5:0
Dyspepsia	0:5	Mild:3	Mod[d]:0	Severe:1	–

[a] 3 episodes of sinus tachycardia, 1 episode of sinus bradycardia, episode of first-degree A-V block

[b] 1 patient died suddenly during the infusion of VCR-EPI on day 2 of his second cycle; not recorded on ECG

[c] MRC scale: 5/5, normal power; 0/5 complete paralysis

[d] Mod, moderate

treatment to a total of five doses per cycle. VCR (0.4 mg absolute) and EPI (12 mg/m^2) were mixed in the same container and infused over 23 h each day for 4 days. Out-patients used the CADD1 pump with its 100-cc cassette. The drugs were dissolved in normal saline to 90 cc total. In-patients employed the bedside "Lifecare System" infusional pump; VCR and EPI were dissolved in the same 500-ml bag of normal saline, which was then infused over 23 h/day. A fresh bag was made up each day. There was no evidence of physico-chemical incompatibility with respect to the VCR/EPI mixtures in either system of infusion.

Patients were also medicated with ranitidine given orally at 150 mg q12h daily, Nystatin given orally at 1 ml (100,000 units) q4h on days 1–10 and allopurinol given orally at 300 mg daily during the first cycle, and then as required. Anti-diabetic agents and prophylactic antibiotics (other than Nystatin) were not employed.

Prior to commencing VEMP, patients underwent a history and physical examination, and the WHO PS was documented. Complete blood counts and differential white cell counts as well as serum calcium, urea, creatinine and immunoglobulin levels were obtained. In the absence of a serum paraprotein, urinary BJP was assayed (one patient). A pre-treatment ECG and an LVEF determination were obtained (although occasionally the LVEF finding could be obtained only after the first cycle). Patients were seen weekly and the same hematological and biochemical determinations were carried out. Muscle power was graded according to the Medical Research Council (MRC) scale ranging from 0 (complete paralysis) to 5 (normal power). The PS was recorded, as were the toxicities encountered (stomatitis, alopecia, diarrhoea, constipation, neurotoxicity, nausea and vomiting), according to WHO criteria [16]. Dyspepsia was recorded as being absent, mild, moderate or severe. An ECG was obtained during each VCR/EPI infusion on the 2nd or 3rd day.

Responses were recorded as complete (CR), partial (PR), progressive disease (PD) or plateau phase. A CR was defined as the absence of a serum and urine M component on conventional electrophoresis in addition to a normal proportion and appearance of plasma cells on bone marrow examination. A PR was defined as a decrease of >50% in the pre-treatment M-component level as determined on two separate occasions ≥4 weeks apart. A sustained rise in the M component in the presence or absence of deterioration in indirect disease parameters (i.e. new lytic lesions, hypercalcemia) constituted PD. The plateau phase was attained in the absence of symptoms attributable to active disease, provided that the serum hemoglobin level was stable and M-component estimations were stable on two occasions ≥3 months apart [7].

Treatment was modified for myelosuppression as follows; if the neutrophil count was $<1.0\times10^9$/l and/or the platelet count was <100,000/l, treatment was deferred for 1 week and given only if both of these parameters improved to these levels. The subsequent EPI dose was reduced by 50% to 6 mg/m^2 per day. If this was tolerated, the next dose was increased by 3 mg/m^2 per day to 9 mg/m^2 per day, which was again increased to 12 mg/m^2 per day if tolerated. If the initially planned dose of 12 mg/m^2 per day was tolerable, the dose was escalated to 15 mg/m^2 per day on the next cycle. (Similar guidelines were established for thrombocytopenia but did not need to be implemented.) The intention was to identify the MTD of EPI, which would be given regularly every 2 weeks. VCR was discontinued for neuropathy and/or constipation of ≥ WHO grade 2.

Results

The 9 patients received a total of 69 cycles of VEMP. A median of 6 cycles/patient were given (range, 1–20 cycles/patient). Excluding the last cycle, 38/60 cycles were of the intended 2-week duration; 22/60 cycles were prolonged by ≥1 week. Among the latter, granulocytopenia accounted for 14 delays (complicated by infection in 7), infection without granulocytopenia caused 5 delays, social reasons caused 2 delays and 1 cycle was delayed for central line insertion. Thrombocytopenia was not dose-limiting; one patient developed grade 3 thrombocytopenia.

The median tolerable dose of EPI given by CI on a 2-weekly basis was 6 mg/m^2 per day × 4 days (range, 3–12 mg/m^2 per day). Only two patients could tolerate 12 mg/m^2 per day and one patient tolerated up to 9 mg/m^2 per day, whereas most patients (five) could receive 6 mg/m^2 per day and one patient, who had had the most prior melphalan treatment, could withstand only 3 mg/m^2 per day. However, there was no simple relationship between the amount of alkylating agent previously received and the MTD of EPI.

The toxicities encountered are listed in Table 2. Five of the nine patients developed peripheral neuropahty severe enough to prompt discontinuation of VCR; sometimes this occurred after only one or two cycles. Stopping VCR seemed to have no obvious effect on the efficacy of the regimen. Most patients experienced mild constipation only, and in only one case was this the reason to stop the VCR. MP was well tolerated in this dose-intensive regimen, although its contribution to the high infection rate could not be ascertained. There were virtually no skeletal muscle sequelae. In two patients the muscle-power score transiently dropped to 4/5 but then recovered fully (5/5) despite the continuation of MP at the intended dose. One patient developed severe dyspepsia, which recovered fully, and three patients developed mild dyspepsia; in all cases, simple medical management was sufficient. Moderate and severe confusion occurred once each, the latter resulting in termination of the treatment. MP was the likely cause. Alopecia was usual for those patients on treatment for more than 1 cycle, but the patient who received 20 cycles completely regrew her hair while on treatment.

ECG recordings, obtained on all patients on the 2nd or 3rd day of nearly every cycle, were unchanged from pre-treatment ECGs in five patients. In the other four pa-

tients, only mild abnormalities were recorded: sinus tachycardia (two cases), sinus bradycardia (one case) and first-degree atrio-ventricular (A-V) block plus sinus tachycardia (one case). All of these abnormalities were transient and of uncertain relationship to the chemotherapy. On serial LVEF assessments, no patient exhibited a drop to $<50\%$. The value for one patient remained at 49% from the onset; that for another patient declined from 74% to 56%, the decrease being of uncertain significance.

Two unexpected deaths occurred, one on the 2nd day of the second cycle and the other on day 5 after completion of the CI in the fifth cycle. In the former case, the cause of death could not be determined. In the latter case, death was due to pneumonia, likely candidial, which developed during a neutropenic episode. The neutrophil count had fully recovered 1 week prior to the patient's death.

Stomatitis, nausea and vomiting were generally mild to moderate and mild diarrhoea occurred in a minority of cases. These side effects were manageable with conventional measures. Infections were a serious and frequent problem. In all, 27 of 69 cycles were complicated by infections (1, grade 1; 16, grade 2; 7, grade 3; 3, grade 4). Largely these infections were caused by attempts to maintain or increase the dose intensity of the regimen, which proved not to be possible. Two cases of oral herpes simplex occurred but resolved satisfactorily; the other infections involved bacterial septicemia and were twice as likely to be associated with neutropenia. Central lines were thought to play an important role in some patients.

In all nine patients, significant declines in levels of serum (or urine) paraproteins occurred. The patient who died during the second cycle almost halved his level but did not live long enough to achieve the formal PR attained by the other eight patients. The duration and quality of these remissions varied; the median duration was 7 months (range, 1–64 + months). No CR occurred, but the patient showing the longest response has enjoyed almost 5 years of symptom-free response in the plateau phase (unmaintained except for a short 3-month course of interferon). All patients ceased treatment with VEMP for various reasons, including attainment of the plateau phase (three patients), development of toxicity in the plateau phase (three patients), development of toxicity in general (one patient) and unexpected death during treatment (two patients). The median survival was 9 months after the start of VEMP treatment (mean, 17 months; range, 1–64 + months).

Paraprotein estimations were obtained weekly whenever possible to determine whether treatment delays were associated with tumor progression prior to the next cycle. We were interested in comparing trends over 2-week periods with trends over 3-week periods (the more usual cycle length in the parent VAMP protocol). Tumor progression for this purpose was defined as a rise of $\geq 10\%$ in paraprotein levels over the post-treatment nadir for that cycle. Information was not complete for each cycle, but in 15 of 49 informative 2-week periods, an adverse rise in paraprotein levels occurred; of 12 informative 3-week periods (i.e. delayed cycles), 10 were associated with an adverse rise in levels of paraprotein. (A few cycles were informative for both 2- and 3-week periods.) This difference was highly significant ($P < 0.002$, Fisher's exact test).

Levels of the normal (i.e. non-paraprotein) immunoglobulins were universally depressed in all patients prior to VEMP treatment, except for the long-term survivor who had a normal IgM (but a low IgA) value. During treatment, these levels tended to remain depressed, but they occasionally ascended into the low-normal range for a short period. IgM levels were more likely to normalize transiently than were IgA levels; five patients experienced transient normalization as measured on eight occasions (IgM) as compared with two patients measured for IgA (one occasion each). The long-term survivor maintained a normal IgM value throghout the study period (but showed a normalization of her IgA level only once).

Discussion

All nine of these patients with alkylator-refractory myeloma experienced a substantial decrease in their paraprotein levels. Only one patient failed to achieve a formal PR because an early, unexpected, sudden death truncated his remission. Five of these eight PRs lasted for ≥ 5 months; one patient remains alive and well at 64 + months. The median MTD of EPI given by CI for 4 days every 2 weeks was 6 mg/m^2 per day; a minority of patients could tolerate up to 12 mg/m^2 per day. VCR had to be stopped in five patients because of a reversible peripheral neuropathy after a median of only two cycles. Stopping VCR did not obviously impair the regimen's efficacy. MP given at 1 g/m^2 per day $\times$ 5 days by 1-h infusion was very well tolerated, causing virtually no myopathy and only occasional confusion and dyspepsia. No technical problem was encountered as a consequence of mixing the EPI and VCR together for 23 h a day in the same container. This regimen could readily be given on an out-patient basis using permanent central lines and portable CI pumps.

The major problem was a high incidence of serious infections, which were observed on at least one occasion in seven of nine patients and were usually accompanied by grade 3 or 4 granulocytopenia. The central venous access devices probably contributed to this toxicity. One of the two unexpected deaths was caused by candidial pneumonia. Generally, however, these infections came under rapid control with broad-spectrum intravenous antibiotics. It was our intent to give EPI at the MTD discovered by dose escalation in each patient; however, our initial starting dose (12 mg/m^2 per day) was too high. It is not possible to determine the relative contribution to this incidence of infection of the anthracycline and the steroid.

Cardiomyopathy did not occur and serious arrhythmias were not recorded during the anthracycline/vincristine infusions despite the regular performance of ECGs. One patient died suddenly on the 2nd day of his second cycle. The cause of death was not established. However, 68 other cycles were given without a similar incident. Serious stomatitis, thrombocytopenia, nausea, diarrhoea and constipation were uncommon. Toxicity was the prime reason for discontinuation in four of nine patients, achievement of the plateau phase was the main reason in three cases, and two patients experienced unexpected death during treat-

ment. No patient actually had a sustained rise in paraprotein levels while on treatment.

Our major goal was to assess the feasibility of giving this variant of the VAD regimen on a bi-weekly schedule. We believe on the basis of this experience that provided the anthracycline dose is individualized at a tolerable level, it is possible to adopt this more frequent schedule. The inconvenience of bi-weekly administration, however, is substantial, and this schedule requires further justification by phase II and III studies. However, our data clearly show that adverse rises in paraprotein levels were much less likely to be encountered in the initial 2 weeks of each cycle than in the 3rd week; we were afforded the opportunity to explore this aspect because occasional cycles were delayed beyond 2 weeks by toxicity.

For this reason, as well as the high response rate obtained in our small series, we believe that a 2-week cycle length is worthy of further exploration in this poor-prognosis group. We do not recommend adoption of this regimen outside of a clinical trial. It is possible to produce comparable survival in alkylator-refractory patients using conventional VAD [3] or even single-agent dexamethasone [2] with less toxicity than we encountered. However, the response rates obtained with VAD (52%) or with single-agent dexamethasone (±24%) in alkylator-refractory patients are lower than the value we obtained (89%), although the small size of our cohort of patients prevents any meaningful conclusion with respect to this particular parameter.

References

1. Alberts DS, Salmon E (1975) Adriamycin (NSC-123127) in the treatment of alkylator-resistant multiple myeloma: a phase II study. Cancer Chemother Rep 59: 345
2. Alexanian R, Barlogie B, Dixon D (1986) High-dose glucocorticoid treatment of resistant myeloma. Ann Intern Med 105: 8
3. Barlogie B, Smith L, Alexanian R (1984) Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med 310: 1353
4. Buzaid A, Durie BGM (1985) Management of refractory myeloma: a review. J Clin Oncol 6: 889
5. Case DC Jr, Ervin TJ, Gams R, et al (1988) Phase I–II study of epirubicin in multiple myeloma. Cancer Res 48: 6246
6. Cersosimo RJ, Hong WK (1986) Epirubicin: a review of the pharmacology, clinical activity and adverse effects of an Adriamycin analogue. J Clin Oncol 45: 425
7. Forgeson G, Selby P, Lakhani S, et al (1988) Infused vincristine and adriamycin with high dose methylprednisolone (VAMP) in advanced previously treated multiple myeloma patients. Br J Cancer 58: 469
8. Gomez GA, Han T, Ozer H, et al (1985) Salvage treatment for patients with multiple myeloma refractory to alkylating agents. Med Pediatr Oncol 13: 325
9. Gore ME, Viner C, Meldrum M, et al (1989) Intensive treatment of multiple myeloma and criteria for complete remission. Lancet II: 879
10. Jackson DV, Case LD, Pope EK, et al (1985) Single agent vincristine by infusion in refractory multiple myeloma. J Clin Oncol 3: 1508
11. Jain KK, Casper ES, Geller NL, et al (1985) A prospective randomized comparison of epirubicin and doxorubicin in patients with advanced breast cancer. J Clin Oncol 3: 818
12. Kyle RA, Greipp PR, Gertz MA (1986) Treatment of refractory multiple myeloma and considerations for future therapy. Semin Oncol 13: 326
13. Praga C (1991) Anthracycline induced cardiotoxicity and its relevance in cancer treatment. In: Nimmo WS, Tucker GT (eds) Clinical measurement in drug evaluation. Wolf, London, p 131
14. Samson D, Gaminara E, Newland A, et al (1989) Infusion of vincristine and doxorubicin with oral dexamethasone as first-line therapy for multiple myeloma. Lancet II: 882
15. Torti FM, Bristow MR, Howes AE, et al (1984) Preliminary observations of the cardiotoxicity of 4′-epidoxorubicin: an evaluation of endomyocardial biopsy. Proc Am Assoc Cancer Res 25: 179
16. WHO (1979) Handbook for reporting results of cancer treatment. Offset publication 48. WHO, Geneva