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Prognostic Value of Clinical, Laboratory, and Histological Characteristics in Multiple Myeloma: Improved Definition of Risk Groups*

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Follow-up data of 320 multiple myeloma (MM) patients entering the German Myeloma Treatment Group (GMTG) trial MM01 were analysed for factors predicting overall (OAS) and tumour related survival (TRS). Response to primary induction chemotherapy was relevant for prognosis if a limit of 25% tumour cell mass (TCM) reduction was used to separate responders from non-responders. Furthermore, TCM, histological grading of myeloma cells, degree of bone marrow infiltration, haemoglobin, platelet counts, calcium, creatinine, albumin, β2M, and Bence Jones proteinuria correlated to both OAS and TRS. Age was relevant for OAS only. The multivariate analysis revealed histological grading, TCM and platelets as the most reliable prognostic factors. Based on these data the Durie/Salmon classification could be improved by defining poor prognosis patients (50% TRS: 16 months) characterised by pretreatment platelets of ≤150.000 and/or poorly differentiated myeloma cell morphology. Patients lacking both risk factors displayed 50% survival times of 46 months in stage III and 88 months in stage II.
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INTRODUCTION

THE SURVIVAL duration of multiple myeloma (MM) patients ranges from a few months to more than 10 years from diagnosis. Numerous studies have been undertaken to define factors of prognostic significance, in order to stratify patients into different risk groups for clinical trials and for general care planning. Several clinical, laboratory, and histological/cytological parameters have emerged, such as age [1–6], performance status [5, 7], factors correlating with tumour load (serum calcium, haemoglobin, M-component in serum and urine, osteolytic lesions) [1–3, 5–9], renal function [1–7], β2-microglobulin (β2M) [1, 2, 4, 9–11], serum albumin [4, 7], thrombocyte [3, 7] and leucocyte counts [7], lactate dehydrogenase [12], plasma cell labelling index [2, 13], myeloma cell morphology and degree of bone marrow infiltration [2, 5, 7, 14–16]. More recently, less well established parameters such as DNA/RNA tumour cell content and DNA hypodiploidy [9, 17], and serum interleukin-2 levels [18], have also been shown to be of prognostic importance. Various items have been combined in several staging systems proposed for defining risk groups in MM, but the significance of the resulting stratification has been questioned [19]. We have recently shown that the calculation of overall survival (OAS) used by the majority of authors, differs markedly from true tumour related survival (TRS) in a malignancy such as MM occurring primarily in the older age group [20]. Respecting this, we have analysed patients' data by univariate and multivariate analyses extending previously published results [20, 21].

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MATERIALS AND METHODS

Patients, treatment and definition of response

Follow-up data from 320 MM patients entering the MM01 trial of the German Myeloma Treatment Group (GMTG) between 1982 and 1986 were analysed. Survival data were available up to the end of 1991. All patients belonged to either stage II or stage III [8] and were randomised for six cycles of either melphalan/prednisone (MP) or vincristine/cyclophosphamide/melphalan/prednisone (VCMP) induction chemotherapy. Tumour response was estimated by the calculation of tumour cell mass (TCM) changes [22]. Responding patients (≥ 25% TCM reduction) received subsequently no or chemotherapy maintenance (for details see ref. 21). Stage I patients were not included because they are not treated by chemotherapy according to GMTG rules but are observed until progress into stage II is unequivocally proven.

Parameters analysed

Causes of death were carefully analysed and were classified as to whether they were tumour-related, i.e. death by MM, MM complications, complications of therapy, or due to disorders other than MM (for details see ref. 20). Between 1982 and the last evaluation in 1991 166 deaths had occurred: 132 MM-related, 22 MM-unrelated, 12 unknown.

The following clinical and laboratory parameters were measured at diagnosis and were evaluated for prognostic relevance:

age, haemoglobin (g/dl), platelet count (n/μl), serum calcium (mmol/l), creatinine (μmol/l), glutamate–pyruvate-transaminase (U/l), alkaline phosphatase (U/l), gamma-glutamyl-transferase (U/l), total serum protein (g/l), albumin (g/l), quantity of the M-component estimated by electrophoresis and serum protein measurement (g/l), type of M-component (IgG, IgA, none), serum β2-microglobulin (β2M) (mg/l) not corrected for kidney function, presence of a Bence Jones protein in the urine, type of Bence Jones protein, osteoporosis, number of osteolytic lesions, and calculated TCM [22].

Two histopathological parameters, myeloma cell grading and extent of bone marrow infiltration were included. Grading was defined by the following criteria resulting in three morphologically defined MM groups [23]: first, well differentiated MM (WD) characterised by >90% mature, <10% polymorphous, and 1% blastic plasma cells; second, intermediate type MM (IM) with >10% mature, >10% polymorphous, and <30% blastic plasma cells; and third, poorly differentiated MM (PD) composed of <10% mature, >10% polymorphous, and >30% blastic plasma cells.

The TCM change after induction chemotherapy were estimated as a post-treatment prognostic parameter.

Statistical methods

Survival calculations were done by the method of Kaplan and Meier [24] differentiating overall (OAS) and tumour-related survival (TRS) [20]. For OAS all cases of death were defined as events. For TRS cases of death due to disorders others than MM were used as censored data. Each patient was considered as alive at the time of his last evaluation, if death had not occurred.

Univariate analysis of prognostic parameters was performed by comparing survival estimates of different patient groups applying the generalised Wilcoxon test. The Cox proportional hazard model was used for multivariate analysis of censored survival data [25].

BMDP (BMDP Statistical Software, Inc., Los Angeles, California, U.S.A.) and SAS (SAS Institute Inc., Cary, U.S.A.) computer software was employed.

RESULTS

Single parameter analysis

Glutamate-pyruvate-transaminase, alkaline phosphatase, gamma-glutamyl-transferase, total serum protein, type and quantity of serum M-component, type of Bence Jones protein, and presence of multiple osteolytic lesions were found to be parameters without prognostic impact on OAS or TRS. Limits discriminating between high and low risk groups, could be defined for haemoglobin, platelet count, serum levels of calcium, creatinine, albumin, and β2M, presence of a Bence Jones protein, TCM, myeloma grading and degree of bone marrow infiltration (Tables 1 and 2, Fig. 1). Patients with a PD myeloma cell morphology or with platelets $\leq 150 \times 10^3/\mu l$ at diagnosis represented a group with a particularly poor prognosis of 13 and 20 months 50% TRS, respectively. Age was a significant prognostic factor for OAS only, but became irrelevant if tumour-related risk was used as the end point.

Different limits of TCM response to induction chemotherapy were tested for prognostic significance. Only a cut-off point of

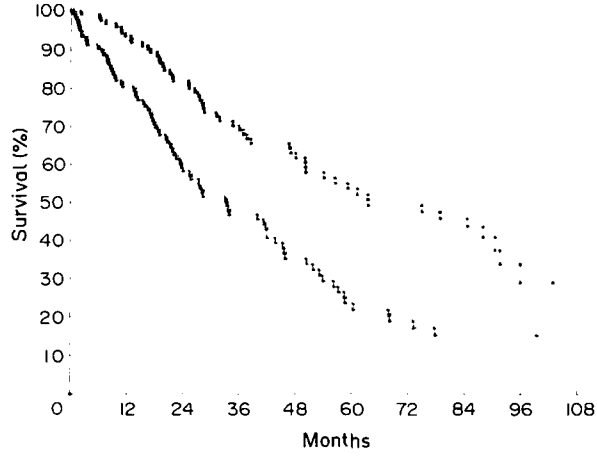

Fig. 1. Tumour-related survival of stage II (----) (n=147) and stage III (——) (n=155) MM patients (P<0.0001).

Table 1. Prognostic indicators for overall survival (OAS) (single parameter analysis)

Parameter	Groups: Definition	Groups: Size (n/n)	50% survival (Months)	P
Age (years)	≤60/>60	127/188	43.3/33.8	0.0509
Haemoglobin (g/dl)	≥10/<10	211/104	45.4/27.2	0.0037
Platelets ($\times 10^3/mm^3$)	≥150/<150	265/46	44.3/18.9	0.0002
Calcium (mmol/l)	≤2.6/>2.6	235/80	50.0/18.8	0.0001
Creatinine (μmol/l)	≤120/>120	228/82	44.3/26.8	0.0006
Albumin (g/l)	≥37/<37	251/62	45.1/25.2	0.0018
β2M (mg/l)	≤6/>6	153/74	44.3/18.1	0.0001
Bence-Jones protein	No/Yes	120/173	49.0/28.2	0.0018
Tumour cell mass ($\times 10^{12}$ cells/m^2)	≤1.2/>1.2	152/162	56.4/26.8	0.0001
Tumour cell grading	WD/IM/PD	96/43/16	55.9/41.7/10.6	0.0001
Tumour cell infiltration of the bone marrow (%)	≤50/>50	81/74	56.4/28.1	0.0053

Table 2. Prognostic indicators for tumour-related survival (TRS) (single parameter analysis)

Parameter	Groups: Definition	Groups: Size (*n*/*n*)	50% survival (Months)	*P*
Haemoglobin (g/dl)	≥10/<10	204/99	58.3/32.7	0.0028
Platelets (×10³/mm³)	≥150/<150	254/45	53.5/20.0	0.0001
Calcium (mmol/l)	≤2.6/>2.6	229/74	55.9/23.9	0.0001
Creatinine (μmol/l)	≤120/>120	220/78	55.9/33.3	0.0001
Albumin (g/l)	≥37/<37	241/60	50.1/27.9	0.0121
β2M (mg/l)	≤6/>6	150/71	53.5/23.4	0.0001
Bence-Jones protein	No/Yes	115/167	56.4/37.7	0.0038
Tumour cell mass (× 10^{12} cells/m²)	≤1.2/>1.2	147/155	63.5/33.6	0.0001
Tumour cell grading	WD/IM/PD	93/41/16	63.4/45.1/13.3	0.0001
Tumour cell infiltration of the bone marrow (%)	≤50/>50	77/72	84.5/39.8	0.0006

25% TCM reduction (in contrast to 50% and 75%) clearly discriminated between patients with good and poor survival (Table 3), both for TRS and OAS as well as for stage II and III subgroups.

Multivariate analysis

All pretreatment factors which had prognostic significance as single parameters (Tables 1 and 2) were entered into a multivariate analysis. Since haemoglobin, bone lesions, calcium, serum M-component and Bence Jones proteinuria are combined for the TCM calculation [8] a separate analysis using all parameters as single items was also performed in order not to underestimate the impact of single factors on survival. Histological bone marrow evaluation and β2M estimates were not available from all patients. Therefore, analyses with or without these parameters resulted in four patient groups of different size: (a) all parameters excluding grading, infiltration volume, and β2M (n=299 for TRS versus n=311 for OAS); (b) all parameters excluding grading and infiltration volume (n=218 versus n=219); (c) all parameters excluding β2M (n=148 versus n=153); (d) all parameters included (n=98, both for TRS and OAS). When TRS was chosen as the endpoint for the calculation with TCM estimates, TCM and platelet count remained as the two most reliable prognostic factors (Table 4). However, in those patients where a detailed histological characterisation of the individual MM had been performed (groups c and d), tumour cell grading appeared together with TCM and platelet count as the most important factors taken up by the Cox model (Table 4). When single parameters were used, several of those items combined in the TCM calculation showed up as being of importance, but again, tumour cell grading ranged highest in all calculations including histological parameters. Age (which was included in every analysis), β2M, and presence of the Bence Jones protein, gained importance only if OAS was used as the endpoint of multivariate analysis (Table 5). Again, tumour cell grading proved to be of importance and showed up as the most important of several prognostic parameters regardless of whether calculated TCM or single parameters only were entered into the Cox model.

Table 3. Tumour cell mass reduction after induction chemotherapy as a prognostic factor for tumour-related survival (TRS)

Tumour cell mass reduction (%)	No. of patients (*n*)	50% survival (months)	*P*
≥25/<25	128/47	68/45	0.0021
≥50/<50	89/86	54/63	n.s.
≥75/<75	55/120	50/68	n.s.

Table 4. Determination of most reliable factors by multivariate analysis (stepwise Cox-regression, endpoint: TRS)

	Using tumour cell mass (TCM):	Using single parameters:
(a)	All parameters excluding grading, infiltration volume, and β2M (n=299);	
	TCM	Calcium
	Platelet count	Haemoglobin
		Platelet count
(b)	All parameters excluding grading and infiltration volume (n=218);	
	TCM	Calcium
	Platelet count	Haemoglobin
		Platelet count
(c)	All parameters excluding β2M (n=148);	
	Grading	Grading
	TCM	Calcium
	Platelet count	Haemoglobin
		Platelet count
(d)	All parameters (n=98);	
	Grading	Grading
	TCM	Calcium
	Platelet count	Platelet count

A staging system based on tumour cell mass, platelet count, and myeloma cell grading

The Durie/Salmon staging system [8] based on TCM calculation has proved a good prognostic parameter for TRS in our

Table 5. Determination of most reliable factors by multivariate analysis (stepwise Cox-regression, endpoint: OAS)

	Using tumour cell mass (TCM):	Using single parameters:
(a)	All parameters excluding grading, infiltration volume, and β2M (n=311);	
	TCM	Calcium
	Platelet count	Haemoglobin
		Platelet count
(b)	All parameters excluding grading and infiltration volume (n=219);	
	β2M	β2M
	TCM	Calcium
	Platelet count	Platelet count
	Age	Age
	Bence Jones protein	Bence Jones protein
(c)	All parameters excluding β2M (n=153);	
	Grading	Grading
	TCM	Calcium
	Platelet count	Haemoglobin
		Platelet count
(d)	All parameters (n=98);	
	Grading	Grading
	β2M	β2M
	Bence Jones protein	Bence Jones protein
	Platelet count	Platelet count
	Age	Age

study (Table 2, Fig. 1). The 50% survival between stage II and III patients differed by 30 months.

Since myeloma cell grading, platelet count, and TCM had turned out as the most reliable parameters determining TRS (Table 4), we have proceeded to combine these items in a heuristic approach towards a better separation of risk groups. A remarkable sharpening of the stratification by TCM alone was thus achieved. First, separating all individuals with an initial platelet count of ≤150.000/μl from stage II and III patients resulted in a poor risk group of patients with a TRS of 20 months, leaving an intermediate group of stage III patients with 42 months TRS and a good risk group of stage II patients with 79 months 50% TRS survival (Fig. 2). The difference between the low and high risk groups was thus enlarged to 59 months. Secondly, when patients with a platelet count ≤150.000/μl and/or PD myeloma cell type were accumulated in the poor risk group, the difference in survival between the poor and good risk groups was expanded to 72 months (Fig. 3). Here the 50% TRS survival was 16 months for the poor risk group comprised of patients with platelet counts ≤150.000/μl and/or a PD MM cell type, whereas the remaining stage III patients survived for 46 months. The good risk group, composed of stage II patients with a WD or IM MM and a platelet count >150.000/μl, displayed a TRS of 88 months, i.e. of more than 7 years from diagnosis.

DISCUSSION

A clear definition of survival is an important prerequisite for an analysis of prognostic factors. In the majority of oncological studies, survival and overall survival are used synonymously,

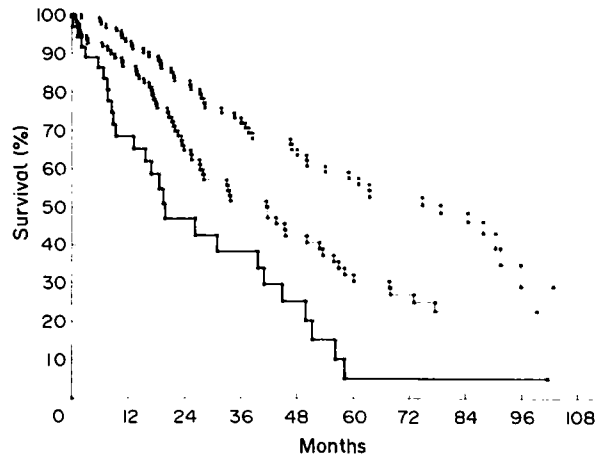

Fig. 2. Tumour-related survival of MM patients with a pretreatment platelet count of < 150.000/μl (——) (n=45), stage II patients with a pretreatment platelet count of ≥150.000/μl (----) (n=127), and stage III patients with a pretreatment platelet count of ≥150.000/μl (——) (n=123) (P < 0.0001).

thus not recognising age as a prognostic factor. Indeed, the results of our study clearly show that age is a factor with prognostic impact for OAS but not for TRS (Tables 1 and 2). For the GMTG study sample, comprising 320 MM patients of stages II and III, mean TRS is 13 months longer than mean OAS [20]. TRS can be determined by correcting OAS using a factor which can be calculated from an age and sex matched control population representing the natural survival probability [20]. Ludwig *et al.* [26] have also shown that if survival is corrected for age, tumour-related survival in MM no longer differs in various age groups. For these reasons, the estimation of TRS provides a better basis of a correct judgement of the patients' disease risk. The controversial discussion [27] whether or not age is a prognostic factor in MM [1–7, 28] can be resolved by recognising TRS as the more correct survival parameter.

Tumour cell grading, the most important histological feature of MM representing its biological properties, has been found to belong to the indicators with the highest probability both regarding OAS and TRS (Tables 1 and 2). This result confirms

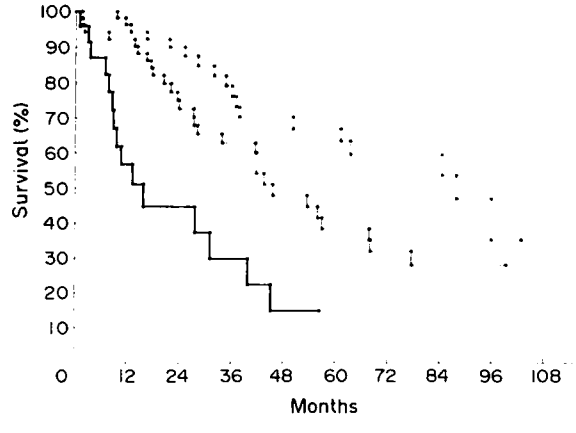

Fig. 3. Tumour-related survival of MM patients with a pretreatment platelet count of < 150.000/μl and/or a PD plasma cell morphology (——) (n=28) and patients deficient for these risk factors of stage II (----) (n=61), and stage III (——) (n=59) (P < 0.0001).

earlier reports by several groups [14–16, 23] who have also shown that histological and/or cytological MM properties are significantly related to prognosis.

Only few multivariate analyses based on biochemical and clinical parameters as well as on bone marrow cytology (degree of tumour cell infiltration [5, 7, 9], morphological grading of bone marrow MM cells [2]) have been performed to-date in MM. The results of our comprehensive study clearly show that among the large number of parameters which were included in the analysis, tumour cell grading, TCM determination, and platelet count remained as the three most reliable prognostic factors.

β2M shown by many authors [1, 2, 4, 9–11] as an outstanding survival parameter, did not show up among the most reliable prognostic factors for TRS (Table 4), in contrast to the calculations using OAS as the end point (Table 5). It has actually been shown in healthy individuals that β2M serum levels are age dependent, rising with increasing age thus depending on the decreasing glomerular filtration rate [29]. So the prognostic impact of β2M serum levels has to be reviewed with respect of this interrelation.

Based on our multivariate analysis, we could improve the prognostic power of the well established Durie/Salmon classification [8] by adding platelet count ($\leq$150.000 versus >150.000) and tumour cell grading (PD versus IM or WD). Patients with a pretreatment platelet count below 150.000/μl and/or a poorly differentiated myeloma cell morphology represent a separate group with a particularly poor prognosis, irrespective of the tumour cell mass (Figs 2 and 3). Cavo *et al.* [3] were first to report the platelet count as a pre-eminent survival parameter, a finding confirmed by our results. Thus, by combining a TCM determination at the time of diagnosis with the platelet count and a standardised grading of MM tumour cells, a given MM patient eligible for treatment (i.e. not belonging to Durie/Salmon stage I) can be assigned to one of three risk groups, a necessary or at least highly desirable information for rational therapeutic decisions.

Another feature of the present investigation concerns the quantitative response to induction chemotherapy, the only post-treatment parameter tested for prognostic significance here (Table 3). In accordance with Palmer *et al.* [30] we did not find any significant correlation between response defined either as a 50% TCM reduction (according to Chronic Leukaemia–Myeloma Task Force) or as 75% TCM reduction (according to Southwest Oncology Group), and survival. Both response definitions which have been widely used in the past, rely on the assumption, that the destruction of a larger fraction of the tumour load will always be of advantage for the treated person. By contrast, a cut-off point at only 25% TCM reduction as used in the GMTG trials, was found to be a valid parameter discriminating between patients of good and poor risk. Although, an easy explanation for this finding is not at hand, one has to assume that the cut-off point of 25% TCM reduction is appropriate to classify the different tumour clones as chemotherapy sensitive and resistant. These qualitative properties are obviously important for the prognosis of the patients. For future trials, we therefore propose that neither 50% nor 75% tumour cell mass reduction should be used any longer for defining remission or treatment failure. By contrast, the earlier decision of the GMTG to use the 25% margin [21] appears to be well justified.

Taken together, our present results which are based on an 8 year prospective observation of patients treated in the MM01 GMTG trial, provide an improved basis for judging patients' risk in MM with respect to survival. Appropriately designed trials are needed to demonstrate whether risk group adapted therapeutic strategies can actually improve the life expectancy of MM patients, particularly with respect to the group of high risk patients which can now be more clearly defined.

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Phase I and Pharmacokinetic Study of Brequinar (DUP 785; NSC 368390) in Cancer Patients

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Brequinar (DUP 785, NSC 368390) is a 4-quinoline carboxylic acid derivative with broad spectrum antitumour activity in experimental models that acts as an antimetabolite by specific inhibition of *de novo* pyrimidine synthesis. We performed a phase I study of brequinar administered as a 10 min intravenous (i.v.) infusion for 5 consecutive days, every 4 weeks. 67 evaluable patients were entered in this study and a total of 130 courses were administered at doses ranging from 2 to 350 mg/m^2. The dose-limiting toxicity was myelosuppression with predominant thromobocytopenia. Myelosuppression was dose-related and non-cumulative, with considerable interpatient variability depending on haematological risk factors. The maximum tolerated dose of brequinar was 210 mg/m^2/day in poor risk patients whereas patients with good risk haematological profile tolerated higher doses (up to 350 mg/m^2/day). Other non-limiting toxicities included nausea and vomiting, mucositis and skin reactions. Brequinar plasma pharmacokinetic profiles were biphasic with alpha half-life ranging from 0.1 to 0.7 h, and beta half-life ranging from 1.5 to 8.2 h. Increase in brequinar area under the plasma concentration versus time curves (AUC) was nonlinear. Day 5 brequinar pharmacokinetics obtained in 21 patients indicated a significant increase in AUC (47%) and half-life beta (133%) compared to day 1 pharmacokinetics in the same patient. Brequinar plasma AUC and the per cent change in platelet count at nadir were correlated ($P < 0.001$). Although no objective response was observed in this study, one minor response was noted in cervical lymph nodes of a Hodgkin's disease patient.
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INTRODUCTION

ORIGINATING FROM the Medicinal Chemistry Section of Dupont Pharma and screened by the NCI Developmental Therapeutics Program, brequinar [Fig. 1; DUP 785; NSC 368390; 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid sodium salt] is a substituted 4-quinoline carboxylic acid which was selected for further investigation because of its preclinical antitumour activity and water solubility [1]. *In vitro*, brequinar was one of the most potent inhibitors of small cell lung and colon cancer cell lines [2, 3]. It also demonstrated high antitumour activity in murine models (L1210 leukaemia, B16 melanoma and colon adenocarcinoma 38) [1, 4] and human tumour xenografts (MX-I breast, LX-1 lung, BL/STX-1 stomach and CX-1 colon carcinomas) [5]. Antimetastatic properties of brequinar were also observed [6].

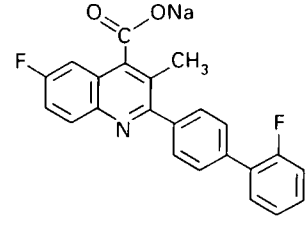

Fig. 1. Chemical structure of brequinar sodium (DUP 785; NSC 368390).

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