Chronic myeloproliferative disorders: prognostic importance of new working classification

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Abstract

Variants of chronic myeloproliferative disorders (CMPD) were compared according to their clinical features and classified by bone marrow biopsy appearances. Subsequently, this classification was further evaluated using survival data and histological variables from iliac crest biopsy specimens of an additional 1391 patients, making a total of 2241 patients available for analysis of outcome. The patients were grouped again into three main classes: "typical"; "variant"; and "transformed". "Typical" comprised the "classic" groups. "Variant" included the less uniform myeloproliferative syndromes, distinguished also by more variable clinical features, a different prognosis, and a greater tendency to fibrotic and blastic transformation. "Transformed" defined the end stages of both "typical" and "variant" types. Ten subgroups were distinguished by different histology and prognosis. Particular prognostic importance was assigned to atypia and immaturity of haemopoiesis, predominance of individual haemopoietic cell line, number and anomalies of megakaryocytes and progressive fibrosis.

It is suggested that the proposed subclassification would be helpful for studies of epidemiology and therapeutic trials by allowing more homogeneous groups to be recognised.

The main groups of chronic myeloproliferative disorders (CMPD), polycythaemia vera,

primary thrombocythaemia, and chronic granulocytic leukaemia (CGL)¹⁻³ are traditionally classified according to characteristic and at least temporarily constant clinical features, and by exclusion of borderline cases. In practice, however, even the "classic" groups show considerable prognostic inhomogeneity.^{4,5} For example, transformation to the fibrotic or blastic stages is hardly predictable, and several variants often have to be lumped together into ill defined groups—for example, agnogenic myeloid metaplasia,⁶ acute myelosclerosis,⁷ and blast crisis.⁸ In our previous study⁹ random biopsy specimens of all untreated patients with CMPD since the year 1960 (including those diagnosed as having "unclassified" CMPD) were analysed by comparing histological and clinical data. The purpose of the present analysis was to test the preliminary results by the use of a greater number of cases and survival data to identify the clinically relevant subgroups (see classification table 1 and revised classification in table 2).

Methods

Iliac crest biopsy specimens from 2241 patients with CMPD (850 untreated and 1391 previously treated) were evaluated by the methodology described in our previous paper,⁹ and the time of survival from biopsy until death or date of last contact were recorded. Observation of these patients started in 1960 and ended in 1985; the mean observation period was 45.3 months, with a minimum of one and a maximum of 303 months. Classification followed the previously defined model,⁹ although the denominations were made more uniform (table 1).

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Table 1 Preliminary histological classification of CMPD with principal sample characteristics

Classes	Main groups	Subtypes	Sample size/n	Mean age (years)	Median survival time (months)
I Typical	Erythrocytic myelosis (Ery-M)	EryGranMeg-M	358	55.9	132.1 ± 4.2
	corresponding to polycythaemia vera	Ery-M	21	58.1	72.7 ± 2.9
	Megakaryocytic myelosis	Meg-M-d (Meg-diffuse)	148	59.8	128.9 ± 1.1
	corresponding to primary thrombocythaemia	Meg-M-c (Meg-clustered)	75	62.1	115.0 ± 2.0
	Granulocytic myelosis (Gran-M)	Gran-M-Meg +	333	54.8	29.5 ± 2.1
II Variant	corresponding to CGL	Gran-M-Meg -	66	48.2	21.1 ± 7.7*
	Erythrocytic myelosis variants corresponding to	EryMeg-M	166	57.9	94.8 ± 13.0*
	borderline polycythaemia vera-primary thrombocythaemia	EryGran-M	80	62.9	57.0 ± 11.0*
	Megakaryocytic myelosis variants corresponding to	Meg-M-i (Meg-immature)	109	55.0	12.3 ± 3.5
	borderline primary thrombocythaemia or cytopenia	Meg-M-p (Meg-pleomorphic)	18	53.8	6.0 ± 1.4
III Transformed	Granulocytic megakaryocytic myelosis corresponding to	GranMeg-M-d (Meg-diffuse)	209	62.0	64.6 ± 4.1
	borderline CGL-primary thrombocythaemia	GranMeg-M-c (Meg-clustered)	228	63.3	49.6 ± 5.5
	Osteomyelofibrosis variants corresponding to myeloid	OMS (Osteomyelosclerosis)	198	60.8	30.3 ± 2.5*
	metaplasia or cytopenia	MF (Myelofibrosis)	48	64.8	15.0 ± 3.5*
	Blastic osteomyelofibrosis variants similar to	B-OMS	24	59.6	6.5 ± 1.2
	malignant myelosclerosis	B-MF	64	61.2	3.8 ± 0.5
	Blastic myelosis variants corresponding to	B-M-mult (multilinear)	43	58.7	10.0 ± 2.6*
	blastic crisis	B-M-un (unilinear)	53	57.0	4.6 ± 1.5*

*Horizontal lines between pairs of data indicate that the difference between the respective means is significant at the 0 = 1% level

Abbreviations

B-M	=	blastic myelosis
B-M-V	=	blastic myelosis variants:
B-M-un	=	blastic myelosis unilinear
B-M-mult	=	blastic myelosis multilinear
B-MF	=	blastic myelofibrosis
B-OMS	=	blastic osteomyelosclerosis
CGL	=	chronic granulocytic leukaemia
CMPD	=	chronic myeloproliferative disorder
Ery-M	=	erythrocytic myelosis
Ery-M-V	=	erythrocytic myelosis variants:
EryGranMeg-M	=	erythro-granulo-megakaryocytic myelosis
EryGran-M	=	erythro-granulocytic myelosis
EryMeg-M	=	erythro-megakaryocytic myelosis
Gran-M	=	granulocytic myelosis
Gran-M-V	=	granulocytic myelosis variants:
Gran-M-Meg -	=	granulocytic myelosis poor in megakaryocytes
Gran-M-Meg +	=	granulocytic myelosis rich in megakaryocytes
GranMeg-M	=	granulo-megakaryocytic myelosis
GranMeg-M-V	=	granulo-megakaryocytic myelosis variants:
GranMeg-M-d	=	granulo-megakaryocytic myelosis with diffuse megakaryocytosis
GranMeg-M-c	=	granulo-megakaryocytic myelosis with clustered megakaryocytosis
Meg-M	=	megakaryocytic myelosis
Meg-M-V	=	megakaryocytic myelosis variants:
Meg-M-d	=	megakaryocytic myelosis with diffuse megakaryocytosis
Meg-M-c	=	megakaryocytic myelosis with clustered megakaryocytosis
Meg-M-i	=	megakaryocytic myelosis with immature megakaryocytosis
Meg-M-p	=	megakaryocytic myelosis with pleomorphic megakaryocytosis

Class I was primarily defined by the accepted criteria (chromosomal analyses were available only in a few cases), and subdivided according to the histological features mentioned above.

Classes II and III were defined by histology alone, with the exception of the PV variants. Pure blastic variants were included only when antecedent CMPD was confirmed; blastic variants combined with typical myelofibrosis or osteomyelosclerosis were generally registered as B-MF or B-OMS, most tracing back to original CMPD. Myelofibrosis and osteomyelosclerosis groups were defined only by those cases in which fibrotic or osteosclerotic changes had already obscured the typical CMPD characteristic. The diagnosis as CMPD was then deduced either from remaining foci of (predominantly megakaryocytic) myeloproliferation or the case history. Cases of CMPD with only minor fibrotic or osteosclerotic changes, including reticular sclerosis, were assigned to their original groups.

Definitions of the various conditions, together with correlations of histological changes with clinical and haematological data, have been given previously.^{5,9,10} The former concerned the different forms of megakaryocytes (normal, dwarf, giant, immature, and pleomorphic), the proliferation, maturity, and predominance of haemopoietic cell lines, and the conditions of reticular sclerosis, myelofibrosis, and osteomyelosclerosis, as well as the correlations of histological changes with clinical and haematological data. The reliability of the histological data had already been assured by at least two observers and the use of at least five differently stained slides.

The survival periods were correlated with the patients' age and sex, the histological subtypes, and the fibrotic and non-fibrotic changes in the biopsy specimen. The data were analysed using BMPD statistical packages.¹¹ Differences between groups were tested for significance using the methods of Breslow¹² and Mantel-Cox.¹³

Table 2 Revised histological classification of CMPD: clinical appearance, age, fibrosis and survival

Classification			Clinical appearance corresponding with	Mean age (years)	Collagenous fibrosis (%)	Median survival (months)
Class I: typical (n = 1001)						
Group	1 Erythrocytic myelosis (Ery-M; EryGranMeg-M)	17%	Polycythaemia vera, typical	56.0	5%	128.8
	2 Megakaryocytic myelosis (Meg-M-d; Meg-M-c)	10%	Primary thrombocythaemia, typical	60.5	13%	124.2
	3 Granulocytic myelosis (Gran-M-Meg +; - Meg -)	18%	CGL, typical	54.8/48.2	19%/9%	29.5/21.1
Class II Variant (n = 683)						
Group	4 Erythrocytic-megakaryocytic myelosis (EryMeg-M)	7%	Polycythaemia vera, primary thrombocythaemia, borderline	57.9	37%	94.8
	5 Erythrocytic-granulocytic myelosis (EryGran-M)	3%	Polycythaemia vera/CGL, borderline	62.4	30%	57.0
	6 Granulocytic-megakaryocytic myelosis (GranMeg-M-d; GranMeg-M-c)	20%	CGL/primary thrombocythaemia, borderline	62.6	46%	56.8
Class III Transformed (n = 557)						
Group	7 Osteomyelosclerosis (OMS)	9%	Myeloid metaplasia or cytopenia	60.8	100%	30.3
	8 Myelofibrosis (MF)	2%	Myeloid metaplasia or cytopenia	64.8	100%	15.0
	9 Blastic myelosis, multilinear (B-M-mult; B-OMS; B-MF)	12%	Blastic crisis or malignant myelosclerosis	57.5	45%	8.8
	10 Blastic myelosis, unilinear (B-M-un)	2%	Blastic crisis	57.0	17%	4.6
		100% =	2.241 cases			

Figure 1a Erythrocytic myelosis (EryGranMeg-M) corresponding to polycythaemia vera: typical trilinear proliferation with incipient cluster formation of megakaryocytes and slight reticular sclerosis. (Gomori's silver impregnation.)

1b Granulocytic myelosis (Gran-M-Meg+) corresponding to CGL: typical granulocytic proliferation with strong increase in dwarf megakaryocytes; incipient transformation into Meg-M-i? (Gallamin blue-Giemsa stain.)

1c Megakaryocytic myelosis (Meg-M-c) corresponding to primary thrombocythaemia: typical proliferation of giant megakaryocytes among otherwise normal haemopoiesis. (Gallamin blue-Giemsa stain.)

1d Granulo-megakaryocytic myelosis (GranMeg-M-c); granulocytic proliferation together with accumulations of giant megakaryocytes in large clusters. (Gallamin blue-Giemsa stain.)

Results

Sixty three per cent of the patients had died; thirty seven per cent were known to be still alive. The longest median survival was 132.1 months (EryGranMeg-M = polycythaemia vera), the shortest 3.8 months (B-MF). The median survivals of patients untreated at the time of biopsy did not differ significantly from those of patients who had already received specific treatment. This applied to all types and subtypes. Moreover, comparative histological evaluation showed no reasons for a separate analysis of treated and untreated patients. The overall ratio between male and female patients was 1.03:1; significant predominance of one sex (female) was found only in mature and immature megakaryocytic myelosis (Meg-M and Meg-M-i).

OVERALL SURVEY (table 1)

The number of patients was higher and the mean age lower in the typical class than in the variant and transformed classes ($n = 1001:810:430$ patients; mean ages = $56.1:60.4:60.6$ years). These figures seem to support the hypothesis that the classes I to III represent sequential stages of CMPD.

Within each class, differences in the median survivals of the main groups were as follows (the symbol > denotes longer than): I: Ery(GranMeg)-M > Gran-M; Meg-M > Gran-M; II: Ery-M-V > Meg-M-i; Gran-M-V > Meg-M-i; III: OMS > B-OMS; OMS > B-M.

Significantly different median survival times were also detected between corresponding pairs of subtypes (different pairs marked

Figure 2 Life table: survivals for three megakaryocytic subtypes of CMPD; A = (Meg-M respectively primary thrombocythaemia); B = (GranMeg-M); C = (Meg-M-i).

Figure 3a Megakaryocytic immature myelosis (Meg-M-i); large sheets of mostly immature megakaryocytes. (Gallamin blue-Giemsa stain.)
3b Myelofibrosis; small groups of immature, partially necrotic megakaryocytes amid fibrotic obliteration of the marrow space. (Gomori's silver impregnation.)
3c Osteomyelosclerosis (OMS); irregular strands of primitive bone, produced by osteoblasts, enclosing islets of haemopoietic bone marrow with numerous giant and necrotic megakaryocytes. (Gallamin blue-Giemsa stain.)
3d Blastic multilinear myelosis (B-M-mult); irregular proliferation of blastic elements of all cell lines, predominantly pleomorphic megakaryoblasts and -cytes, and collagenous fibrosis. (Gallamin blue-Giemsa stain.)

Figure 4 Life table: survivals for four transformed subtypes of CMPD; A = osteomyelosclerosis (OMS); B = myelofibrosis (MF); C = blastic multilinear myelosis (B-M-mult); D = blastic unilinear myelosis (B-M-un) grouped together with blastic osteomyelosclerosis (B-OMS), and blastic myelofibrosis (B-MF).

by horizontal lines): thus Gran-M-Meg+ > Gran-M-Meg-, in spite of the lower mean age of the latter group; and EryMeg-M > EryGran-M. In the latter case the second group was older, but not enough to explain the different life spans; OMS > MF (once again age alone could not explain the difference in life expectancy); B-M-mult > B-M-un (while the mean ages of these groups were almost the same).

COMPARISON OF SURVIVAL TIMES OF SUBTYPES (ACCORDING TO PREDOMINANT CELL LINES)

Erythrocytic predominance

Median survival times of EryGranMeg-M were equal to that of typical polycythaemia vera. Moreover, of the variant subtypes of polycythaemia vera, the survival times for

EryMeg-M (fig 1a), differed from those of EryGran-M; $p = 0.0001$ (Breslow and Mantel-Cox tests). Pure Ery-M comes closer to the variant subtypes in this respect, although the group was too small for statistical evaluation.

Granulocytic predominance

Patients with Meg- subtype of Gran-M showed shorter median survival times than those with Gran-M-Meg+, the latter being equal to that of typical CGL (fig 1b) ($p = 0.0001$ in both Breslow and Mantel-Cox tests). The latter group also survived for a shorter time than patients with EryGran-M ($p = 0.02$, Breslow test; and $p = 0.004$, Mantel-Cox test), and than those with Gran-Meg-M ($p = 0.0001$, Breslow and Mantel-Cox tests). These variant groups did not differ from each other in this respect.

Figure 5 Life table: correlation of fibrotic changes and survival of 1955 patients with CMPD (including all subtypes except OMS, B-OMS, and B-MF).

Table 3 CMPD subtypes: fibrosis and survival

Subtype	Degree of fibrosis						Level of significance for differences in median survivals	
	None or reticular sclerosis			Collagenous fibrosis				
	n	Mean age	Median survival	n	Mean age	Median survival	Breslow p value	Mantel-Cox p value
Erythrocytic myelosis (EryGranMeg-M)	340	54	134	18	56	46	0.0001	0.0009
Megakaryocytic myelosis (Meg-M-c)	52	61	*	23	64	82	0.079	0.034
Granulocytic myelosis (Gran-M-Meg +)	270	53	32	62	63	22	0.015	0.055
Erythrocytic megakaryocytis myelosis (EryMeg-M)	105	56	130	61	62	71	0.01	0.0002
Granulocytic megakaryocytic myelosis (GranMeg-M-c)	165	62	74	42	64	39	0.03	0.01
Megakaryocytic immature myelosis (Meg-M-i)	52	55	20	57	55	8	0.04	0.01
Blastic myelosis	30	60	12	12	57	3	0.04	0.05

75th quantile: 55 months = more than 50% of patients alive during control time.

Megakaryocytic predominance

Here the differences in median survival times in the subtypes are most noteworthy, as can be observed from the life table in fig 2: Meg-M (fig 1c) > GranMeg-M > Meg-M-i (fig 3a).

Transformation

The transformed fibrotic and blastic variants are compared in the life table (fig 4), and in figs 3b-d. Life expectancy decreased in the following order: OMS > MF > B-M-mult > B-OMS and B-M-un.

CORRELATION BETWEEN FIBROSIS, AGE, AND SURVIVAL

There were only 130 cases (with a mean age of 55 years) in which no fibrotic changes were evident at all; most (n = 1289 with a mean age 57 years) exhibited reticular sclerosis; 468 (mean age 61 years) presented focal to moderate degrees of collagenous fibrosis; osteomyelosclerosis was diagnosed in 198 patients (mean age 60.8 years), and myelofibrosis in 48 patients (mean age 64.8 years). Fibrosis was in general associated with a worse prognosis (fig 5).

On the other hand, increasing age diminishes the life expectancy in chronic disorders, and especially in CMPD: 807 of the patients with a mean age of 42 years had a median survival of 74 months, against 55 months for a mean age of 62 years (n = 726); p=0.02 Breslow, p=0.0007 Mantel-Cox, and 27 months for mean age of 73 years (n = 688). These differences were also significant (p=0.0001, Breslow and Mantel-Cox). There

was, however, a pronounced tendency for fibrosis among the subtypes: thus fibrosis was most frequently absent in Meg-M-d; reticular sclerosis was most common in Ery(GranMeg)-M and Gran-M; and collagenous fibrosis was very evident in the clustered subtypes of Meg-M and GranMeg-M and in Meg-M-i.

The significant correlations between the median survival times and fibrotic changes on the one hand, and age on the other, were both positive in most groups (tables 3 and 4). Statistical congruence (using the χ^2 test) between age and degree of fibrosis, however, was manifest in only two subtypes—namely, Gran-M-Meg+ and EryMeg-M. These variables diverged considerably from one another in Meg-M-i, myelofibrosis and B-M-mult, in which the detrimental influence of fibrosis dominated, and in GranMeg-M-d, in which age, not degree of fibrosis, was the major indicator of poorer life expectancy.

REVISED PROGNOSTIC CLASSIFICATION

As a result of the above findings, it was necessary to revise our previous scheme of prognostic classification as follows (table 2): 10 groups of CMPD were distinguished primarily by their histology and prognosis and assigned to three classes:

Class I ("typical") was characterised by the uniform connection between the well known histological changes and clinical symptoms with a moderate tendency to transformation.

Class II ("variant") was defined by the less uniform proliferation of more than one cell

Table 4 CMPD subtypes: age and survival

Subtype	Age						Level of significance for differences in median survivals	
	Younger patients			Older patients				
	n	Mean age	Median survival	n	Mean age	Median survival	Breslow p value	Mantel-Cox p value
Erythrocytic myelosis (EryGranMeg-M)	183	46	171	173	66	97	0.0001	0.0001
Megakaryocytic myelosis (Meg-M-d)	73	49	*	73	71	79	0.003	0.0003
Granulocytic myelosis (Gran-M-Meg +)	168	41	35	160	69	23	0.0002	0.0003
Erythrocytic megakaryocytic myelosis (EryMeg-M)	87	48	136	79	68	66	0.0001	0.0001
Granulocytic megakaryocytic myelosis (GranMeg-M-d)	111	52	95	98	73	36	0.0002	0.0001
Granulocytic megakaryocytic myelosis (GranMeg-M-c)	123	56	71	104	72	33	0.0001	0.0001
Osteomyelosclerosis (OMS)	100	52	42	94	70	22	0.0002	0.0005
Myelofibrosis (MF)	25	57	11	23	74	25	0.32	0.18

*75th quantile: 55 months = more than 50% of patients alive during control time.

line with intermediate clinical symptomatology (compared with the "classic" groups), and noticeable instability.

Class III ("transformed") comprised the fully developed fibrotic or blastic variants of I and II, and a small subgroup of possibly "primary" osteomyelosclerosis and myelofibrosis with a (sub)chronic course. The secondary origin and acute to subacute course of the immature and pleomorphic megakaryocytic myeloses resemble the "blastic crises" of other haemopoietic cell lines. As they are generally combined with multilinear haemopoietic proliferation and have a strong tendency to fibrosis, they were integrated into group 9. Collagenous fibrosis in class I varies from 5–19%, in class II from 30–46%, and in class III from 17–100% of the cases.

Discussion

The detection of the clonal origin of CMPD¹⁴ has contributed to our understanding of its diversity of phenotypes and transformations, which by far exceeds the accepted standards. Moreover, we are beginning to understand some of the consequences of uncontrolled myeloproliferation for the local organisation of cellular production and release, such as the fibrotic sequelae of excess megakaryocytopoiesis.^{15,16} It is now also evident that cell line specific symptoms of CMPD have different influences on the time and mode of the final collapse. In the light of these findings the total spectrum of CMPD was analysed primarily from the aspect of the structural pathogenesis at the site of its origin, the bone marrow. This attempt was supported by a 25 year database of technically uniform iliac crest biopsy specimens including case controls, clinical findings, and survival data. Biopsy specimens of previously treated patients were included, because treated and untreated groups did not differ significantly from each other, as has also been found by other authors.¹²

Class I adds a more precise histological scale to the well defined diagnostic criteria of the typical CMPD groups. It becomes clear that isolated proliferation of every haemopoietic cell line has its characteristic prognosis, provided that release of the mature cells into the blood is unimpaired: the most inert form of proliferation is megakaryocytic, followed by erythrocytic, and ultimately granulocytic proliferation as the most unfavourable. Erythrocytic-erythraemic proliferation, however, is rare and its association with polycythaemia vera dubious. In accordance with published findings,^{14,17–22} the life expectancy of the trilinear proliferation of polycythaemia vera was found to surpass the rest of CMPD, possibly due to its proximity to healthy bone marrow activity. The consistent longevity of Meg-M contrasts with some previous data^{3–5} which might be due to bias as a result of the inclusion of thrombocythaemic cases belonging to other subgroups. The considerable reported variation in survivals of patients CGL^{4,5,23–31} could have been caused

by the different life expectancies of the Gran-M-Meg+ and -Meg- subgroups, and the previously neglected identification of GranMeg-M, more correctly classified under group 6. This group is also known as "chronic megakaryocytic-granulocytic myelosis (CMGM)", and included considerable numbers of Ph¹ positive cases.³² Prognostic importance has also been attributed to dysplasia and immaturity of haemopoiesis in CGL.^{33–35} Such cases were excluded from our Gran-M groups. The more malignant course of the eosinophilic variants and their tendency to rapid fibrosis and immature megakaryocytosis have been evaluated previously.¹⁰

Class II variants are characterised by their comparatively uniform prognosis (by which the class differs significantly from the others), the higher proportions of fibrotic cases, and by the ambivalent cellularity of the blood. Groups 4 and 5 are regarded as variants of polycythaemia vera; group 6 resembles CGL histologically, but may be distinguished clearly from it by megakaryocytosis of the giant and not the dwarf type. Groups 4 and 5 are generally preceded by polycythaemia vera; whereas group 6 may develop de novo or from groups 2 and 3.⁹ A further reason for the distinction of the variant groups is their different tendency to blastic or fibrotic transformation.¹⁰

Class III comprises the transformed variants, understood as the naturally irreversible final stages of the other subgroups.¹⁰ Myelofibrosis, however, may develop into osteomyelosclerosis; both may acquire blastic dedifferentiation; and blastic forms may become fibrotic. The distinction of myelofibrosis from osteomyelosclerosis, requiring a biopsy specimen of ample size, is important not only in view of the different prognosis, but also in terms of different pathogenesis. Osteomyelosclerosis can no longer be regarded merely as the more advanced stage of myelofibrosis.^{9,15} It may proceed together with myelofibrosis from the very beginning, or it may never develop during the course of myelofibrosis, or it may take a slower course of its own, possibly triggered by a specific (as yet unknown) osteoblast-activating factor.

Common presages of myelofibrosis and osteomyelosclerosis are the clustered foci of megakaryocytes, observed mostly in groups 1, 2, and 6. These early signs of inefficient megakaryocytopoiesis are followed by the accompanying accumulations of necrotic megakaryocytes and dislocated platelets. Their detrimental effects are most conspicuous when held up against the good prognosis of diffuse megakaryocytosis with safe release of excess platelets. Common presages of unilinear granulocytic blastosis and of immature, pleomorphic, or blastic megakaryocytosis are groups 3 and 5.⁹ Additional studies are required to evaluate the prognosis of the individual cell line forming the B-M-un group. Erythro- and megakaryoblastic crises generally involve more than one cell line and tend to develop into progressive fibrosis; they

are both classified into group 9 because of similar prognosis and treatment, but are differentiated from unilinear blastic crises (group 10). Primary "acute myelosclerosis" is not distinguished by histology from group 9.

The overall survey of CMPD shows that the course of the disorder depends primarily on the degree of cellular differentiation and the type of the cell lines involved, but much more on the former. Additionally, the involvement of one or more cell lines in itself is a valuable indicator for diagnosis and prognosis. Further prognostic factors are fibrosis and age. The rigid definition of myelofibrosis and osteomyelosclerosis results in shorter survivals for these groups and allows us to analyse the prognostic influence of minor degrees of fibrosis in the other subtypes.^{49 10 36-}

⁴⁰ In this way it became evident that reticular sclerosis is not correlated with later osteomyelosclerosis and myelofibrosis, while collagenous fibrosis from its initial focal stages indicates progressive fibrosis. The different prognostic role of fibrosis and age in the subgroups is another argument for the meticulous histological analysis of CMPD. Moreover, it is important to know that this very common procedure has substantial diagnostic and prognostic value of its own.

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