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MYELODYSPLASIA IN CHILDHOOD

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Two simple statements can be given which reflect our helplessness with respect to myelodysplasia:

- MDS are rare in childhood, but features and course of disease resemble those in adults.
- JCMML should be considered as a pediatric subtype of MDS, but with a worse prognosis than CMML in adult patients.

MDS = Myelodysplastic syndrome
JCMML = Juvenile chronic myelomonocytic leukaemia

INTRODUCTION

Myelodysplastic syndrome (MDS) is a term rarely used in pediatric literature. Although the various disease entities have been defined by the FAB cooperative group /3/, synonyma like preleukemic syndrome, subacute or smoldering leukemia, refractory anemia, childhood monosomy 7 syndrome, juvenile chronic myelocytic leukemia (JCML), chronic myelomonocytic leukemia (CMML) are still used for MDS classification.

Other reasons why the pediatrician is not so familiar with this group of diseases are its low incidence, lacking awareness of the problem and the absence of clear diagnostic criteria. MDS is said to encompass approximately 1-2 % of acute leukemia cases /9/. On the other hand JCML accounts for 0,5-2 % of all leukemias /3/. It is therefore not surprising that even in the most recent literature few data are available and only small series of patients are described /4, 7, 9, 17, 25, 26/.

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There is still a lot of controversy regarding the distinction of myeloproliferative from myelodysplastic diseases and in particular regarding the use of the terms JCML and MDS /1, 8, 16, 22/. Pediatricians distinguish Ph+ chronic myelocytic leukemia (CML) (the so called adult type) from the juvenile type of CML /21/. The latter disease is characterized by the lack of the Ph chromosome, by its manifestation in children under 5 years of age, by the presence of thrombocytopenia, often elevated hemoglobin F(HbF), the poor response to treatment and by a short survival time (no more than one or two years).

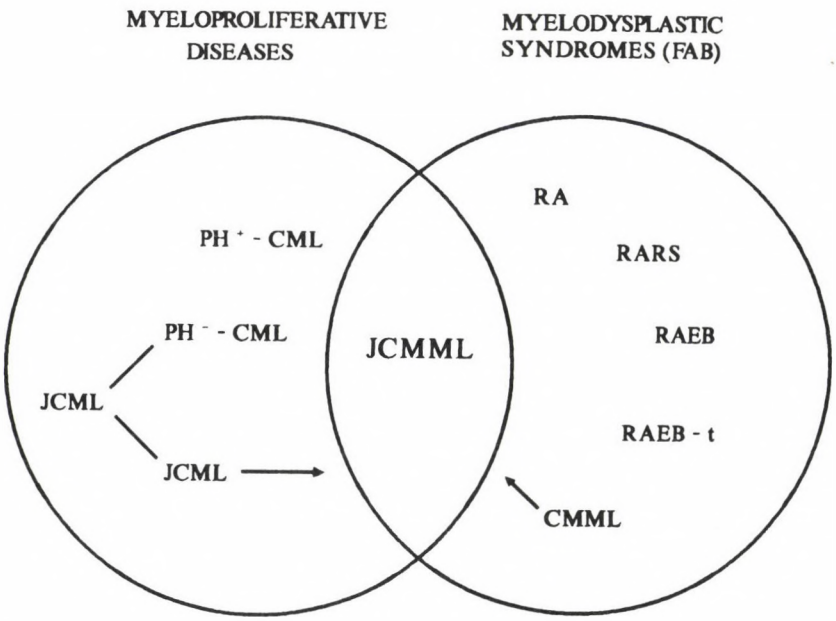

Fig. 1. FAB - French-American-British co-operative Group;
PH±-CML - Philadelphia pos./neg. chronic myeloic leukemia;
CMML - chronic myelomonocytic leukemia;
JCML - juvenile CML;
JCMML - juvenile CMML;
RA - refractory anemia;
RARS - refractory sideroblastic anemia;
RAEB - RA with excess of blasts;
RAEB-t - RAEB in transformation;

Applying the criteria proposed by the FAB group to define the MDS subtype CMML, which usually occurs in elderly patients, the clinical and hematological findings do not resemble those of JCML. Therefore it seems acceptable to consider JCML a special form of CMML and to introduce the term juvenile chronic myelomonocytic leukemia (JCMML) (Fig. 1).

PATIENTS AND METHODS

Clinical and hematological findings in JCMML

In 1984, Castro-Malaspina et al /8/ published a survey of 38 patients treated at the Hospital St.Louis in Paris and the Memorial Sloan Kettering Cancer Center in New York. The age distribution showed that the majority of these children were under 4 years at diagnosis, the predominating age being the first and second year of life. The male sex clearly prevailed.

The main symptoms and clinical findings were failure to thrive, fever, recurrent infections and bleeding tendency with anemia. Frequently children showed variable papular and ekzematoid skin rashes especially of the face. In addition to generalized lymphadenopathy most of the children presented with hepatosplenomegaly. The small series collected during the last 8 years in our own institution demonstrated very similar features (Table I).

Hematologically a leukocytosis of usually not more than 100.000/ul was characteristic with the presence of immature granulocytes in the peripheral blood. In all these cases a monocytosis of over 1500/ul was present. Often few blasts and red cell precursors in the peripheral blood were encountered, accompanied by a low hemoglobin, elevated HbF concentration and thrombocytopenia. Usually an increase of gamma-globulins and a higher lysozyme titer are detected in the serum also /8/.

Clinical and hematological findings in MDS

As it was mentioned, pediatric experience in MDS is very limited. In the recently published article of Creutzig et al. /9/ data on 21 children were collected from several institutions in Germany and Italy. 16 were diagnosed as RAEB in transformation, 4 as RAEB and 1 as adult type CMML. During the last 8 years we saw 5 cases in Austria. 1 child had RA, 3 had RAEB and 1 patient RAEB -t. There was also a clear prevalence of males, but the disease manifestation occured in a higher age group than JCMML (Table II). The patients' characteristics resembled those in adults. Long history, not necessarily an organ involvement and blood pictures of great variability with or without the presence of blasts. HbF and leucocyte alkaline phosphatase score were not always pathologic.

Bone marrow findings and chromosomal abnormalities in JCMML and MDS

Bone marrow cellularity and number of blasts varied markedly but signs of dysplasia were always present in at least one of the three cell lineages /7, 9, 25/.

TABLE I

Symptoms and clinical findings at diagnosis in JCMML

Symptoms and Clin. Findings	Castro-Malaspina et al (Cancer 54, 675, 1984) (N=38)	Own Pts. (N=6)
o Sex	26 ♂, 12 ♀	5 ♂, 1 ♀
o Age	0-6 yrs (most < 4 yrs)	3 MTS - 3 3/12 yrs
o Malaise and Failure to thrive	23 (60 %)	6/6
o Rec. infections	22 (58 %)	5/6
o Bleeding	19 (50 %)	4/6
o Cutaneous manifestations	16 (42 %)	5/6
o Lymphadeno-pathy	8 (21 %)	6/6
o Hepatospleno-megaly	34 (89 %)	6/6

Comparing bone marrow smears of JCMML and MDS we could not find any striking differences concerning cellularity, number of blasts and megakaryocytes or cytochemistry. The dysplasia was more pronounced in MDS and atypical monocytoid cells were more common in JCMML. In all our cases the immunological phenotyping showed the prevalence of a myelomonocytic population in JCMML, as evidenced by the presence of the epitop CDw14 in 25 - 70 % of cells.

Neither stem cell cultures nor chromosome analyses could clearly discriminate between both disease groups. As the result of a clonal defect the colony-forming capacity of all of the marrow hemopoietic precursor cells is quite low or absent in the majority of MDS patients in adulthood, this is also true for the diseases in childhood /13/. Besides an impaired growth of normal hematopoietic progenitors an excessive proliferation of monocyte macrophage colonies in the absence of exogenous colony-stimulating activity were detected in some cases of JCMML /1, 11/, an observation that was not shared by our small number of patients.

TABLE II

Patients characteristics in MDS in childhood

	Creutzig et al. (1987)	Own Pts.
No of Pts.	21	5
Sex	12 ♂ 9 ♀	4 ♂ 1 ♀
Age (Median)	2 - 17 yrs (11 2/12 yrs)	4 8/12 - 14 11/12 yrs
RA	-	1
RAEB	4	3
RAEB-t	16	1
CMML	1	-
Duration of History (Weeks)	1 - 32 (10)[1]	3 - 24 (8)[1]
Hepatomegaly	12/21 (57 %)	2/5
Splenomegaly	4/21 (19 %)	3/5
Lymphadenopathy	5/21 (24 %)	3/5
Bleeding	8/21 (38 %)	1/5
WBC (x 10^9/l)	0,8-27,0 (5,5)[1]	1,5-22.5 (11,8)[1]
Hemoglobin (g/dl)	3,8-12,9 (7,8)[1]	8,7-11,7 (8,9)[1]
Platelet Count (x 10^9/l)	6 -141 (37)[1]	42-50 (78)[1]
Blasts (%)	1 - 26	0- 7
Fetal hemoglobin ↑	5/ 9 (56 %)	1/3
Lap* Score ↓	3/ 9 (33 %)	0/2

* leucocyte alkaline phosphatase

1 median

Out of 6 patients with JCMML one patient each showed a monosomy 7 and a trisomy 8, one further patient developed a 7p+ anomaly in blast crisis. Two out of 5 patients with MDS had also a monosomy 7 and one patient a 11 q - deletion.

Surveying the data in the literature, there is a surprising similarity of chromosomal abnormalities detected in MDS and JCMML /9, 12, 14, 15, 19, 27/. In both disease groups monosomy 7 and trisomy 8 are most frequently encountered. So far it seems unlikely that other possible changes are typical for one or the other group (Table III).

TABLE III

Chromosome anomalies in childhood MDS

MDS
o No Anomalies (Approx. 40 %)
o Monosomy 7
o Trisomy 8
o Other changes (5q-, 11q, 18q-)
JCMML
o No anomalies (~ 80 %)
o Monosomy 7
o Trisomy 8
o Other anomalies (chromosomes 1, 3, 5, 8, 15, 17, Y)

DISCUSSION

Prognosis and treatment

The prognosis of JCMML is poor. 26 out of 38 patients in the series of Castro-Malaspina et al. /8/ died within 2 years, irrespectively of the treatment (25 of them had received chemotherapy). Only 12 patients survived more than 2 years. The development of acute leukemia was the cause of death in 11 patients. We had a similar experience in our small group of

patients: 4 out of 6 died between 5 and 45 months after diagnosis due to progressive disease and/or therapy related septicemia (median 15 months). All had received several treatment schedules, 3 children were also splenectomized. In 3 patients, alfa-Interferon (alfa-INF)- treatment was unsuccessful except for a transient response of 4 months in one case /20/. Two children are living with stable disease 5 and 12 months, respectively, after diagnosis.

The survival statistics clearly show the bad prognosis of MDS in childhood. Only 5 out of 21 patients in the cohort of Creutzig et al /9/ were alive between 16 to 69 months after diagnosis (3 of them in complete remission) and the median survival was 20 months (1-69+ months). The benefit of intensive chemotherapy remains doubtful in these series. 2 out of 5 of our own patients developed a leukemic transformation 5 and 7 months, respectively, after diagnosis. 2 children died after a survival time of 2 and 22 months, respectively 3 patients are in stable disease without treatment 1, 1 and 23 months after diagnosis.

So far it is not clear what kind of treatment can be recommended in JCMML and MDS /23/. Clinical observation without chemotherapy but with support of blood products seems to be the treatment of choice. The median time until progression in the entire group of Creutzig et al /9/ was 12 months (range 1-21 months). A low dose chemotherapy with 6-mercaptopurine or cytosine arabinosid did not show convincing results /5, 7, 9/.

Intensive chemotherapy may be of certain value for inducing remission (generally of short duration) in progressive disease /6, 9, 24/. 11 out of 21 patients in the series of Creutzig et al. /9/ were treated with intensive chemotherapy, 6 of them achieved complete remission. Only casuistic experiences are reported with alfa-INF up till now /10, 20/. Only one of our 3 patients showed a transient response at a dose of 2×10^6 U/day s.c. Allogenic matched bone marrow transplantation is certainly the treatment of choice for eliminating the underlying stem cell defect.

Approximately 30 patients including children with MDS have been transplanted since 1979, two third of which are still in remission /2/.

REFERENCES

1. Altmann AJ, Palmer CG, Baehner RL: Juvenile "chronic granulocytic" leukemia: A panmyelopathy with prominent monocytic involvement and circulating monocyte colony-forming cells. Blood 43: 341, 1974

2. Appelbaum FR, Storb R, Ramberg RE, et al.: Treatment of preleukemic syndromes with bone marrow transplantation. Blood 69: 92, 1987

3. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, Sultan C: Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 51: 189, 1982

4. Berndt MC, Kabral A, Grimsley P, Watson N, Robertson TI, Bradstock KF: An acquired Bernard-Soulier-like platelet defect associated with juvenile myelodysplastic syndrome. Br J Haematol 68: 97, 1988

5. Bolwell BJ, Cassileth PA, Gale RP: Low dose cytosine arabinoside in myelodysplasia and acute myelogenous leukemia: A review. Leukemia 1: 575, 1987

6. Chan HSL, Estrov Z, Weitzmann SS, Freedman MH: The value of intensive combination chemotherapy for juvenile chronic myelogenous leukemia. J Clin Oncol 5: 1960, 1987

7. Cantu-Rajnoldi A, Porcelli P, Cattoretti G, Ferrari M, Romitti L, Adamoli L, Masera G: Myelodysplastic syndromes in children: Observations on five cases. Eur J Paediatr Haematol Oncol. 1: 71, 1984

8. Castro-Malaspina H, Schaison G, Passe S, Pasquier A, Berger R, Bayle-Weisgerber Ch, Miller D, Seligmann M, Bernard J: Subacute and chronic myelomonocytic leukemia in children (juvenile CML). Cancer 54: 675, 1984

9. Creutzig U, Cantu-Rajnoldi A, Ritter J, Romitti L, Odenwald E, Conter V, Riehm H, Masera G: Myelodysplastic syndromes in childhood. Am J Pediatr Hematol/Oncol 1987

10. Elias L, Hoffman R, Boswell S, Tensen L, Bonnem M: A trial of recombinant alpha 2 interferon in the myelodysplastic syndromes: I.Clinical results. Leukemia 1: 105, 1987

11. Estrov Z, Grunberger T, Chan HSL, Freedman MH: Juvenile chronic myelogenous leukemia: Characterization of the disease using cell cultures. Blood 67: 1382, 1986

12. Ghione F, Macucci C, Symann M, Michaux JL, Casteels-Van Daele M, Van Den Berghe H: Cytogenetic investigations in childhood chronic myelocytic leukemia. Cancer Genet Cytogenet 20: 317, 1986

13. Greenberg PL: In vitro culture techniques defining biological abnormalities in the myelodysplastic syndromes and myeloproliferative disorders. Clin Haematol 15: 973, 1986

14. Gyger M, Bonny Y, Forest L: Childhood monosomy 7 syndrome. Am J Hematol 13: 329, 1982

15. Hagemeijer A, Hählen K, Smit Van Zanen GE: C-group chromosome abnormalities in bone marrow cells of three children with dyshaematopoiesis of unknown origin. Br J Hematol 46: 377, 1980

16. Hamblin TJ, Oscier DG: The myelodysplastic syndrome - a practical guide. Hematol Oncol 5: 19, 1987

17. Horsman DE, Massing BG, Chan KW, Kalousek DK: Unbalanced translocation (1;7) in childhood myelodysplasia. Am J Hematol 27: 174, 1988

18. Hutter JJ, Hecht F, Kaiser-Mccaw B, Hays T, Baranko P, Cohen J, Durie B: Bone marrow monosomy 7: Hematologic and clinical manifestations in childhood and adolescence. Hematol Oncol 2: 5, 1984

19. Michiels JJ, Mallios-Zorbala H, Prins MEF, Hählen K, Hagemeijer A: Simple monosomy 7 and myelodysplastic syndrome in thirteen patients without previous cytostatic treatment. Br J Hematol 64: 425, 1986

20. Mutz I, Zoubek A: Transient response to alpha-interferon in juvenile chronic myelo-monocytic leukemia. Eur J Pediatr Hematol/Oncol 5: 71, 1988

21. Smith KL, Johnson W: Classification of chronic myelocytic leukemia in children. Cancer 34: 670, 1974

22. Spiers ASD: Philadelphia-chromosome-negative chronic myelocytic leukaemias. In: Chronic granulocytic leukaemia, ed. MT Shaw, Praeger Publishers p 231, 1982

23. Tricot G, Boogaerts MA: The role of aggressive chemotherapy in the treatment of the myelodysplastic syndromes.Br J Haematol 63: 477, 1986

24. Tricot G, Lauer RC, Appelbaum FR, Jansen J, Hoffman R: Management of the myelodysplastic syndromes. Semin Oncol 14, 444, 1987

25. Van Wering ER, Kamps WA, Vossen JM, Van der List-Nuver CJA, Theunissen PMV: Myelodysplastic syndromes in childhood: Three case reports. Br J Haematol 62: 137, 1985

26. Wegelius R: Preleukaemic status in children. Scand J Haematol 36: 133, 1986

27. Weiss K, Stass S, Williams D, Kalwinsky D, Dahl GV, Wang W, Johnson FL, Murphy SB, Dow LW: Childhood monosomy 7 syndrome: Clinical and in vitro studies. Leukemia 1: 97, 1987

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