Occurence of a myelodysplastic syndrome (MDS) during first-line 2-chloro-deoxyadenosine (2-CDA) treatment of a low-grade gastrointestinal MALT lymphoma. Case report and review of the literature

While myelodysplastic syndrome (MDS) and acute leukemia (AL) are well-known secondary diseases after administration of chemotherapy, particularly with alkylating agents, they have only rarely been reported in the context of purine analogue treatment. In all cases an interval of several months has been observed until onset of the secondary disease and cytogenetic analyses showed typical chromosomal aberrations. In this case report a 68-year-old male Caucasian with low-grade lymphoma developed a MDS during ongoing first-line treatment with the purine analogue 2-CDA (Cladribine). Furthermore a normal karyotype was present, initially and at all consecutive control evaluations. Thus, this case represents another rare report of an evolution of purine analogue treatment-associated MDS and the absence of cytogenetic aberrationes might suggest a different mechanism in the pathogenesis of this secondary disease.

Haematologica 2004; 89:(1)e1-e3

Purine analogues show a marked activity in the treatment of indolent Non-Hodgkin's lymphomas (NHL).[1,2,3] Their toxicity is primarily hematological: reversible neutropenias, anemias and thrombocytopenias of WHO-toxicity grade 3 and 4 as well as an increased infection rate due to treatment related T-cell suppression have been described.[4,5] While MDS and AL are well-known secondary complications of chemotherapy, particularly with alkylating agents, comparable changes in the course of treatment with purine analogues have only rarely been reported and in all cases an interval of several months has been observed between treatment and onset of the secondary disease. Furthermore, whenever analysed all reviewed cases display cytogenetic aberrations characteristic for secondary MDS/AL.

Case report

A 68-year-old male Caucasian was diagnosed with low-grade MALT lymphoma of the sigmoid colon and the stomach in June, 1997. Bone marrow biopsy as well as cytology revealed normocellular marrow without infiltration or any sign of dysplasia. In the course of a clinical trial,[6] Helicobacter pylori was eradicated and treatment with 2-CDA started. The patient received a dose of 0.12 mg/kg body weight on 5 consecutive days, administered as a two-hour infusion. A second course was given starting on day 29. At that time a slight increase in MCH, as well as in mean corpuscular volume (MCV) was noted. At day 12 after Cladribine infusion a temporary bicytopenia was observed with a white blood cell (WBC) count of 1.6×10^9/L and a platelet (Plt) count of 116×10^9/L. With further increased MCH (36.1 pg) and MCV (103.2 fl) values but otherwise normal blood counts, a third course of chemotherapy was administered at day 58. Again, as in the second course, WBC and Plt counts dropped on day 12 (2.3×10^9/L and 101×10^9/L, respectively). In addition hemoglobin decreased to 116 g/L. The peripheral blood parameters, however, failed to recover as they did during the second course. Hemoglobin values continuously decreased to transfusion dependency. Plt counts dropped to an average of 40×10^9/L, and MCH and MCV continuously raised up to 41.0 pg and 121.0 fl, respectively. Since hemolysis parameter were negative a bone marrow biopsy and cytologic aspiration were carried out revealing a normocellular marrow with hypercellular erythropoesis, erythroid precursors showing either multinuclearity and/or nuclear budding and a moderately increased iron content. The most striking bone marrow finding was an increased number of myeloid blasts accounting for approximately 30% of total nucleated cells. Thus, these findings fulfilled the French-American-British-classification (FAB) criteria for MDS, subtype refractory anemia with excess of blasts in transformation (RAEB-t). Interestingly, chromosomal analysis showed no abnormalities. Two and 14 months later, a rebiopsy was carried out confirming the initial findings. Regarding the lymphoma, the staging procedure revealed a complete remission.

At present, the peripheral blood counts are still unchanged displaying a pronounced bicytopenia with a hemoglobin value around 90 g/L and a Plt count of 60×10^9/L. Since control bone marrow biopsy still exhibited RAEB-t with a normal karyotype only supportive care measures have been employed so far.

Therapy-related MDS and AML in literature (see also Table 1)

Pretreated cases

The majority of publications describing therapy-associated MDS and AML following purine analogues treatment report on cases with a history of previous administration of at least one other cytotoxic drug, in most instances first line treatment with alkylating agents.[7-12]

In all cases the onset of MDS was delayed. So far indicated in the literature the intervall between treatment and first sign of MDS or AML was 5 to 24 months. Cytogenetic analysis was performed in five of the puplished cases revealing chromosomal aberrations typical for secondary MDS/AML. In a case of chronic lymphocytic leukemia (CLL), initially treated with alkalating agents, MDS and subsequently AML emerged 18 month after second line treatment with 6 cycles of Fludarabine (FA). Whereas a normal karyotype was initially present in the bone marrow specimen, a trisomy 8 evolved in the course of transformation to overt AML.[10] In a second patient, suffering from mantle cell lymphoma, previously treated with chlorambucil, developement of AML (FAB-M5) was diagnosed 19 months after completing 2 cycles of 2-CDA. Cytogenetics were characterized by complex aberrations.[11] In a third patient, suffering from (unspecified) NHL MDS with monosomia 7 could be detected 15 months after completing further treatment with 2-CDA.[11] First line chemotherapy consisted of cyclophosphamide, doxorubicin, vincristine, prednisone and chlorambucil in this case. Robertson *et al.*[12] retrospectively analysed more than 1300 patients with CLL treated between 1972 and 1992. Seven patients initially treated with chlorambucil and prednisone developed MDS or AML. Two of them additionally received FA or FA followed by two cycles of VAD (vincristine, doxorubicine and dexamethasone) and developed RAEBt and RARS 14 and 24 months, respectively after onset of therapy. Multiple cytogenetic aberrations including monosomia 5 and 7 could be demonstrated in both cases.

First line treated cases with concomitant administration of purine analogues and alkylating agents

Morrison et al.[13] reported on five cases of secondary disease following concomitant first line treatment of B-CLL with 4-11 cycles of fludarabine and chlorambucil. The

Table 1. Literature review and present case.

Reference	*Age/sex*	*Initial Diagnosis*	*Prior Treatment*	*Purine analogue (no. of cycles)*	*Bone marrow disease*	*Cytogenetic aberrations*	*Interval (months)*
Present report	68/m	MALTom	0	2-CDA (3)	MDS (RAEBt)	46xy	0
Morrison *et al.* (2002)	49/m	B-CLL	0	FA (12)	MDS (ns)	nm	51
Misgeld *et al.* (2001)	64/f	Ig NHL	0	FA (6)	MDS (ns) > AML?	multa incl. -7, -5	18
Van den Neste *et al.* (1999)	62/f	LPCL	0	2-CDA (9)	MDS (RAEB)	multa incl. -7	31
Van den Neste *et al.* (1999)	73/f	WD	0	2-CDA (2)	MDS (RAEB)	multa incl. -7, -5[b]	11
Kroft *et al.* (1997)	49/nm	CLL	0	2-CDA (5)	MDS (RARS)	-7	16
Laurencet *et al.* (1997)	29/m	FLM	0	2-CDA (5)	MDS (RA)	46xy > incl. -7 ,+8[c]	14
Morrison *et al.* (2002)	60/f	B-CLL	0	FA + A (6)	MDS (RARS) > AML	multa incl. -5	27
Morrison *et al.* (2002)	44/f	B-CLL	0	FA + A (5)	AML	nm	30
Morrison *et al.* (2002)	57/m	B-CLL	0	FA + A (7)	MDS (ns)	mult.	34
Morrison *et al.* (2002)	72/f	B-CLL	0	FA + A (11)	AML	multa incl. -7, -5	35
Morrison *et al.* (2002)	54/m	B-CLL	0	FA + A (4)	MDS (RAEB)	nm	53
Robertson *et al.* (1994)	61/m	B-CLL	A	FA (nm) > VAD(2)	MDS (RAEBt)	multa incl. -7, -5	24
Robertson *et al.* (1994)	70/m	B-CLL	A	FA (nm)	MDS (RARS)	multa incl. -7, -5	30
Delannoy *et al.*. (1999)	nm	WD	yes, no A	2-CDA (nm)	MDS (ns)	nm	nm
Delannoy *et al.* (1999)	nm	WD	nm	2-CDA (nm)	MDS (ns)	nm	nm
Delannoy *et al.* (1999)	nm	WD	A	2-CDA (nm)	MDS (ns)	nm	nm
Schlaifer *et al.* (1994)	72/f	WD	A	FA (2), 2-CDA (1)	MDS (ns) > AML	nm	nm
Orchard *et al.* (1998)	nm	SLVL	yes, nm	FA (5)	MDS (ns)	nm	7
Orchard *et al.* (1998)	nm	CLL	yes, nm	FA (4)	MDS (ns)	nm	5
Orchard *et al.* (1998)	nm	CLL	yes, incl. A	FA (6)	MDS (ns)	nm	7
Orchard *et al.* (1998)	nm	CLL	yes, incl. A	FA (6)	MDS (ns)	nm	8
Orchard *et al.* (1998)	nm	NHL	yes, incl. A	FA (9)	MDS (ns)	nm	7
Frewin *et al.* (1997)	73/m	CLL	yes, A	FA (6)	MDS (RAEB) > AML	8	18
Kong *et al.* (1998)	nm	NHLd	yes, A	2-CDA (nm)	MDS (ns)	-7	15
Kong *et al.* (1998)	57/m	MCL	yes, A	2-CDA (2)	AML	mult[a]	19

[a] :multiple cytogenetic abnormalities; [b] :cytogenetic abnormalities 6 weeks after treatment with chlorambucil; [c] :about 7 months following radiation; d :advanced indolent lymphoma; A: alkylating agents; FL: Follicular lymphoma WHO grade 1 or 2; FLM: Follicular mixed,small cleaved cell B-non Hodgkin`s lymphoma; incl.: including; LPCL: Lymphoplasmacytic lymphoma; MCL: Mantle cell lymphoma; nm: not mentioned; ns: not specified; SLVL: Splenic lymphoma with villous lymphocytes; VAD: vincristine, doxorubicine, dexamethasone; WD: Waldenström's disease; >: denotes a chronological order

patients developed MDS (n=2), AML (n=2), or MDS evolving to AML (n=1) after an interval of 27 to 53 months. Cytogenetic analysis was performed in three patient and revealed complex cytogenetic abnormalities in all cases, including monosomia of chromosome 5 in two of them and an additional loss of chromosome 7 in one.

First line treated cases without prior or concomitant administration of alkylating agents

Compared to reports of MDS and secondary AML following treatment with alkylating agents and concomitant or consecutive purine analogues treatment, monotherapy with purine analogues without prior chemotherapy leading to secondary MDS or AML are even rarer. To date, only six cases are reported in the literature, four of them treated with 2-CDA and two with FA.

Kroft *et al.*[14] describes a patient with CLL stage Rai IV receiving 5 cycles of 2-CDA. The patient entered complete remission, but MDS with monosomia 7 was diagnosed 18 months later. Laurencet *et al.*[15] published a history of a 29 year old patient with follicular lymphoma displaying pancytopenia as early as 5 months after termination of 5 cycles of 2-CDA. Cervical radiation was carried out and follow up investigations including a bone marrow biopsy revealed MDS with complex karyotypic aberrations (monosomia 7 and trisomia 8).

Two further cases are provided by Van den Neste *et al*:[16] The first patient, suffering from indolent lymphoma received 9 cycles of 2-CDA and was diagnosed with MDS/RAEB three years after therapy. Again, monosomia 7 was detected by karyotype analysis. In the second case - the underlying disease was Morbus Waldenström - myelodysplastic features characteristic of MDS/RARS with a normal karyotypic pattern arose 11 months after finishing 2 cycles of 2-CDA. Due to disease progression monotherapy with Chlorambucil was initiated which ultimately led to the progression of the RARS to a RAEB subtype with complex karyotypic alterations including monosomia 7.

Finally, two more cases of MDS after first line treatment with FA are reported. One case is outlined by Misgeld *et al.*[17] A 64 year old woman with low grade lymphoma developed MDS 18 months after treatment with 6 cycles of FA. Cytogenetic analysis revealed complex abnormalities. The second case was described by Morrison *et al.*[11] A 49 year old male patient with B-CLL was treated with 12 cycles of FA, resulting in the development of MDS 51 months later.

Discussion

MDS and AL are well-known complications of chemotherapy, especially with alkylating agents. As purine analogues are incorporated into DNA, they potentially interfere with DNA repair mechanisms, thereby inducing prolonged immunosuppression with extremely low CD4 cell counts.[4,5] Thus, an increased incidence of secondary malignancies is expected. However, only few cases of secondary diseases, particularly MDS and AL following purine analogue therapy are reported in the literature and in most of those cases purine analogues were used as second line treatment, mostly after primary therapy with alkylating agents.[7-12] In addition, cases of secondary malignancies following first line monotherapy with purine analogues are extremely rare and only six cases have been reported to date.[12-16] The purine analogue Cladribine was used in four cases (14-16) and FA[13,17] in two of them; the time period between therapy and onset of MDS were several months. All analysed cases featured a cytogenetic aberration, including monosomia of chromosome 7 and/or 5.

Interestingly, in contrary to all cases reported in literature so far, our patient developed MDS during an onging first-line treatment and no cytogenetic aberration was

present. This might suggest a different mechanism in the pathogenesis of this secondary disease. Although the number of reported cases in literature is quite small, one should consider purine analogue therapy as potentially leukemogenic, and thus, - especially in case of a preceeding or concomitant therapy with alkylating agents - be aware of the higher risk of inducing a secondary MDS or AL.

Gerald Jäger,[1] Gerald Höfler,[2] Werner Linkesch,[1] Peter Neumeister[1]

[1]Department of Internal Medicine, Division of Haematology, [2]Institute of Pathology Karl-Franzens-University, Auenbruggerplatz, Graz, Austria

Correspondence: Gerald Jäger, M.D.,
Division of Haematology, Department of Medicine, Karl-Franzens University, Auenbruggerplatz 38, 8036 Graz, Austria
Tel. +43 316 385 4086 Fax. +43 316 385 4087
E-mail gerald.jaeger@uni-graz.at

Key words: Myelodysplastic syndrome, purine analogues, first-line treatment

References

1. Spiers AS, Parekh SJ, Bishop MB. Hairy-cell leukemia: induction of complete remission with pentostatin (2'-deoxycoformycin). J Clin Oncol. 1984; 2: 1336-42.
2. Keating MJ, O'Brien S, Lerner S, Koller C, Beran M, Robertson LE, Freireich EJ, Estey E, Kantarjian. H. Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. Blood. 1998; 15; 92: 1165-71.
3. Rummel MJ, Chow KU, Jager E, Leimer L, Hossfeld DK, Bergmann L, Peters HD, Hansmann ML, Meyer A, Hoelzer D, Mitrou PS. Intermittent 2-hour-infusion of cladribine as first-line therapy or in first relapse of progressive advanced low-grade and mantle cell lymphomas. Leuk Lymphoma. 1999; 35: 129-38.
4. Cheson BD. Infectious and immunosuppressive complications of purine analog
therapy. J Clin Oncol. 1995; 13: 2431 – 48.
5. Seymour J, Kurzrock R, Freireich EJ, Estey EH. 2-CDA induces durable remissions and prolonged suppression of CD4+ lymphocyte counts in patients with hairy cell leukemia. Blood. 1994; 15;83: 2906-11.
6. Jäger G, Neumeister P, Brezinschek R, Hinterleitner T, Fiebiger W, Penz M, Neumann HJ, Mlineritsch B, DeSantis M, Quehenberger F, Chott A, Beham-Schmid C, Höfler G, Linkesch W, Raderer M. Treatment of Extranodal Marginal Zone B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue Type With Cladribine: A Phase II Study. J Clin Oncol 2002 Sep 15;20(18):3872-7
7. Delannoy-A, Van den Neste-E, Michaux-JL, Bosly-A, Ferrant-A, Cladribine for Waldenstrom's Macroglobulinaemia, Br J Haematol. 1999 Mar;104(4):933-4.
8. Schlaifer-D, Rigal-Huguet-F, Brousset-P, Delannoy-A, Bosly-A, Secondary neoplasms in two patients treated with purine analogues. Nouv Rev Fr Hematol. 1994 Aug;36(4):341.
9. Orchard J-A, Bolam S, Oscier DG. Association of myelodysplastic changes with purine analogues. Br J Haematol. 1998; 100: 677-9.
10. Frewin-RJ; Provan-D; Smith-AG , Myelodysplasia occurring after fludarabine treatment for chronic lymphocytic leukaemia, Clin-Lab-Haematol. 1997 Jun; 19(2): 151-2
11. Kong-LR, Huang-CF, Hakimian-D, Variakojis-D, Klein-L, Kunzel-TM, Gordon-LI, Zanzig-C, Wollins-E, Tallman-MS, Long term follow-up and late complications of 2-chlorodeoxyadenosine in previously treated, advanced, indolent non-Hodgkin's lymphoma. Cancer. 1998 Mar 1;82(5):957-64.
12. Robertson-LE, Estey-E, Kantarjian-H, Koller-Ch, O`Brian-S, Brown-B, Keating-MJ, Therapy-related leukemia and myelodysplastic syndrome in chronic lymphozytic
leukemia. Leukemia 1994 Dec;8(12): 2047-51
13. Morrison VA, Rai KR, Peterson BL, Kolitz JE, Elias L, Appelbaum FR, Hines JD, Shepherd L, Larson RA, Schiffer ChA. Therapy-related myeloid leukemias are observed in patients with chronic lymphocytic leukemia after treatment with fludarabine and chlorambucil: Results of an intergroup study, Cancer and Leukemia Group B 9011.
J Clin Oncol. 2002; 20: 3878-84.
14. Kroft SH, Tallman MS, Shaw JM, Thangavelu M, Peterson LC. Myelodysplasia following treatment of chronic lymphocytic leukemia (CLL) with 2- chlorodeoxy-adenosine (2-CdA). Leukemia. 1197; 11: 170.
15. Laurencet FM, Zulian GB, Cabrol Ch, Betticher DC. Myelodysplastic syndrome with biclonal monosomy 7 and trisomy 8 after treatment with cladribine (2-chloro-2-deoxyadenosine) and involved field radiation therapy. Cancer Genet Cytogenet. 1997; 99: 85-9.
16. Van-Den-Neste E, Louviaux I, Michaux JL, Delannoy A, Michaux L, Hagemeijer A, et al. Myelodysplastic syndrome with monosomy 5 and/or 7 following therapy with 2-chloro-2'-deoxyadenosine. Br-J-Haematol. 1999; 105: 268-70.
17. Misgeld E, Germing U, Aul C, Gattermann N. Secondary myelodysplastic syndrome after fludarabine therapy of a low-grade non-Hodgkin's lymphoma. Leuk Res. 2001; 25: 95-8.