



Chromosomal abnormalities in secondary MDS and AML. Relationship to drugs and radiation with specific emphasis on the balanced rearrangements

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ABSTRACT

Background and Objective. In therapy-related myelodysplasia (t-MDS) or acute myeloid leukemia (t-AML) balanced chromosome aberrations to bands 11q23 and 21q22 have been significantly related to previous chemotherapy with DNA topoisomerase II inhibitors. The purpose of the present study was to evaluate to what extent other balanced chromosome aberrations show the same association, and to evaluate a possible relationship to patient age and subgroups of drugs.

Design and Methods. All previously published cases of t-MDS and t-AML with any type of balanced aberration identified from Felix Mitelman's *Catalog of Chromosome Aberrations in Cancer* were analyzed for age and type of previous therapy, and the results were evaluated in univariate and multivariate analyses.

Results. A total of 422 cases were recorded, 328 had previously received well specified types of chemotherapy; 254 presented one out of five characteristic balanced aberrations, whereas 168 cases presented different uncharacteristic balanced aberrations. In univariate analysis cases with translocations to 11q23 had most often received DNA topoisomerase II inhibitors, whereas patients with the uncharacteristic balanced rearrangements most often had received alkylating agents ($p < 0.00000001$). Inv(16), t(15;17), and t(9;22) were likewise significantly associated with previous therapy with DNA topoisomerase II inhibitors and to almost the same extent as translocations to 21q22. Patients with translocations to 11q23 were significantly younger as compared to all other groups of patients. Translocations to 11q23 predominated following therapy with epipodophyllotoxins, whereas patients with translocations to 21q22, inv(16), t(15;17), and t(9;22) most often had received anthracyclines. In a multivariate analysis taking age into consideration, however, these drug-specific associations were no longer significant.

Interpretation and Conclusions. Specific balanced chromosome aberrations in t-MDS and t-AML involv-

ing chromosome bands 11q23 and 21q22, inv(16), t(15;17), and t(9;22) are all significantly associated with previous therapy with DNA topoisomerase II inhibitors, as compared to the uncharacteristic balanced aberrations most commonly observed after therapy with alkylating agents. Younger age and not a specific type of DNA topoisomerase II inhibitor seems to predispose specifically to development of t-MDS and t-AML with translocations to chromosome band 11q23.

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Key words: therapy-related MDS, therapy-related AML, balanced chromosome aberrations, DNA topoisomerase II inhibitors

The cytogenetic abnormalities observed in a major proportion of patients with MDS and AML *de novo* have aroused much interest during recent years as being an important, possibly the most important, prognostic determinant¹⁻⁴ directly reflecting some of the genetic changes responsible for leukemic transformation.⁵⁻⁷ However, our knowledge is still limited as to why and how these chromosome aberrations arise and how far each single abnormality represents a more or less important event at an early or later stage in the multistep process of malignant transformation. For further studies of these problems, secondary or therapy-related MDS (t-MDS) and AML (t-AML) may represent an important model.

The first study demonstrating a close association between exposure to a specific group of cytostatic agents and development of t-MDS and t-AML with specific chromosome aberrations was published in 1977 by Rowley *et al.*⁸ In a study of 10 patients treated for malignant lymphomas with alkylating agents and irradiation, loss of whole chromosomes no 5 and/or no 7 was observed in nine patients. Subsequent studies confirmed these findings and also demonstrated that deletions of various parts of or loss of the whole long arms of chromosomes #5 and #7 are highly characteristic⁹⁻¹⁴ and present at the earliest diagnosis of the disease. In addition, other types

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of unbalanced aberrations with chromosomal loss were commonly observed in t-MDS and t-AML, including deletions of various parts of the short arms of chromosomes #12 and #17 and loss of a whole chromosome 18.⁹⁻¹⁴

A gain of chromosomal material was observed less often in t-MDS and t-AML. Primarily, trisomy 8 was observed, this aberration being the most common in patients with AML *de novo*.¹⁻⁴ In patients with t-MDS and t-AML, however, +8 was often observed as part of a complex karyotype and in only a subclone of cells or as an evolutionary event;¹³ For these reasons +8 may represent a less important step in leukemic transformation. Trisomy 1q and trisomy 21q were the only other, rather commonly observed aberrations with gain of chromosome material, mainly originating from the unbalanced translocation t(1;7)(p11;q11) with the presence of two normal chromosomes no 1 and a simultaneous loss of a normal chromosome #7⁹⁻¹⁵ and from various unbalanced translocations to chromosome 21.¹⁵ Cases of t-MDS and t-AML with balanced aberrations such as the t(8;21)(q22;q22), the inv(16)(p13q22), the t(15;17)(q22;q12) and the translocations involving chromosome band 11q23, frequently observed in AML *de novo*, were in the earlier studies of t-MDS and t-AML rather rare and most often considered as incidental cases of *de novo* leukemia rather than being directly therapy-induced.

Simultaneously with the chromosome studies, the whole group of alkylating agents was demonstrated as leukemogenic in well-defined cohorts of patients treated for various malignancies, with relative risks in the range of 100-300,¹⁵ if compared to the risk of AML in the general population. These results indicate a close association between the chemotherapy and the development of leukemia with chromosome defects, as the disease in almost all patients with t-MDS and t-AML following intensive therapy with alkylating agents must be supposed to be directly therapy-induced. In many of the studies, radiotherapy, whether administered alone or combined with chemotherapy, was demonstrated to add little if anything to the risk of leukemia.

The first studies suggesting that other types of recurrent chromosome aberration could be specifically associated with different types of chemotherapy came from studies indicating that the epipodophyllotoxins are leukemogenic.^{16,17} In these studies leukemias with abnormalities of chromosome no 11 were common. The results were confirmed in many subsequent studies, and furthermore some cases with balanced translocations involving band 21q22 were observed.¹⁸ It was thereafter shown that other DNA topoisomerase II inhibitors such as the anthracyclines,^{19,20} mitoxantrone,²¹ and some dioxypiperazine derivatives²² are leukemogenic. Finally, in two larger series of consecutive cases of t-MDS and t-AML, balanced translocations involving chromosome bands 11q23 and 21q22

were significantly associated with previous therapy with DNA topoisomerase II inhibitors.^{23,24} Based on a review of the literature we suggested that also other specific balanced chromosome aberrations less commonly observed in t-MDS and t-AML, such as the inv(16) and the t(15;17), could also relate to previous therapy with DNA-topoisomerase II inhibitors.^{25,26} In consequence, it was considered that t-MDS and t-AML could serve as a more general model for the development of chromosome abnormalities and MDS and AML.

In children with t-AML following epipodophyllotoxin in therapy of acute lymphoblastic leukemia (ALL), balanced translocations involving chromosome band 11q23 totally predominate,¹⁷ whereas therapy with anthracyclines in only a few pediatric cases has been followed by t-AML with balanced translocations involving band 21q22.²⁷ Following therapy of Chinese patients for psoriasis with the drugs Bimolane and ICRF 154, both of them DNA topoisomerase II inhibitors, t-AML with t(15;17) predominated, although some cases with t(8;21) were also observed.²² However, these associations of specific chromosome aberrations to specific subtypes of drug belonging to the DNA topoisomerase II inhibitors were not supported by our previous study of Caucasian adults.²³ We observed an almost even distribution of translocations involving the chromosome bands 11q23 and 21q22 in t-AML following the various subgroups of DNA topoisomerase II inhibitors. It remains therefore an open and important question, to what extent different DNA topoisomerase II inhibitors induce t-MDS and t-AML with different balanced chromosome aberrations, or to what extent the cytogenetic differences relate to other factors, primarily age and race.

Materials and Methods

To solve the question of a specific association between subgroups of drugs and development of t-AML with specific balanced chromosome aberrations, we reviewed all previously published cases of secondary leukemia with any type of balanced aberration. These cases were identified from Felix Mitelman's *Catalog of Chromosome Aberrations in Cancer*,²⁸ where cases of secondary leukemia are specifically indicated, to which we added our own review of the literature. The following parameters were recorded: patient age, sex, type of primary tumor, type of previous treatment including radiotherapy and/or chemotherapy with registration of single drugs, presentation of the disease as t-MDS or t-AML and the cytogenetic characteristics. All data were primarily evaluated in univariate and subsequently in multivariate analysis to examine possible relationships between clinical parameters, type of leukemia and karyotype abnormalities. A total of 422 cases with t-MDS and t-AML were identified presenting balanced chromosome aberrations and with adequate clinical information. Patients who had received more than one drug belonging to the DNA topoisomerase II

inhibitors and patients presenting more than one balanced aberration were excluded in the specific analyses of these parameters, in order to establish the effect of each specific drug and each chromosome aberration. Significant correlations in univariate analyses were evaluated by the Chi-square test and Fisher's exact test, and subsequently a multivariate analysis was performed based on a log-linear model.

Results

Table 1 shows the relationship between type of previous therapy for the primary tumor and the development of t-MDS or t-AML with various specific and other non-specific balanced chromosome aberrations for all 422 patients identified from the literature. Thirty-nine patients had previously received radiotherapy only, 119 had received alkylating agents, in many cases combined with radiotherapy but without DNA topoisomerase II inhibitors, 134 had received DNA topoisomerase II inhibitors plus alkylating agents and in some cases also radiotherapy, 75 patients had received DNA topoisomerase II inhibitors alone or in combination with cisplatin or other drugs not previously demonstrated as leukemogenic and in some cases radiotherapy, and 55 patients had received other drugs or less well specified therapy for their primary tumor.

If only those patients previously treated with chemotherapy are considered, translocations involving chromosome band 11q23 were predominantly observed following therapy with DNA topoisomerase II inhibitors, 77/83 cases, whereas only a smaller fraction of patients with the other uncharacteristic balanced aberrations, 36/117, had received these drugs ($p < 0.0000001$). As far as cases of t-MDS and t-AML with translocations involving chromosome band 21q22 as well as the whole group with the three other characteristic balanced aberrations are concerned, namely inv(16), t(15;17) and t(9;22), these aberrations were likewise observed significantly more often in patients treated with DNA topoisomerase II inhibitors, namely 37/49 cases and 59/79 cases, respectively, as compared to only 36/117 patients with the other uncharacteristic balanced aberrations ($p = 0.0000003$ and < 0.0000001 , respectively).

Table 2 shows the relationship between patient age and development of t-MDS or t-AML with the various characteristic and the whole group of uncharacteristic balanced chromosome aberrations for all 422 patients. Seventy-seven patients were younger than 20 years whereas 319 were 20 years of age or more. A specific association between age and type of balanced aberration was only observed for patients with translocations involving band 11q23, as these were younger, below 20 years, significantly more often as compared to the whole group of four other characteristic balanced chromosome aberrations ($p < 0.0000001$) or the uncharacteristic balanced chromosome aberrations ($p < 0.0000001$).

Table 3 shows the association between the specific subtype of DNA topoisomerase II inhibitor administered in previous therapy of 152 patients who developed t-MDS or t-AML and various balanced chromosome aberrations, including only patients treated with one of the drugs belonging to this group. Ninety patients had previously received anthracyclines, 42 patients epipodophyllotoxins, 6 mitoxantrone and 14 dioxypiperazine derivatives. If the anthracyclines and the epipodophyllotoxins are compared first, balanced translocations involving chromosome band 11q23 predominated following therapy with the epipodophyllotoxins: 25/48, whereas only a minority of patients with t-MDS or t-AML who showed the other characteristic or uncharacteristic balanced

Table 1. Relationship between general type of therapy for primary tumor and development of t-MDS or t-AML with different balanced chromosome aberrations.

Aberration	General Type of Treatment for the Primary Tumor				
	RT only	Alkyl±RT	Alkyl+ATTOP±RT	ATTOP±RT	Others/Unknown
11q23	4	6	47	30	8
21q22	2	12	20	17	6
inv(16)	1	6	2	2	3
t(15;17)	11	6	11	14	3
t(9;22)	2	8	17	3	3
Others	19	81	27	9	32
Total	39	119	134	75	55

Abbreviations: RT denotes radiotherapy; ATTOP, DNA topoisomerase II inhibitors; others, other uncharacteristic balanced chromosome aberrations. p values were calculated by Fisher's exact test (two sided).

- 1) versus 4) : 77/83 versus 36/117, $\chi^2 = 73.44$, $p < 0.0000001$.
- 2) versus 4) : 37/49 versus 36/117, $\chi^2 = 26.27$, $p = 0.0000003$.
- 3) versus 4) : 59/79 versus 36/117, $\chi^2 = 34.67$, $p < 0.0000001$.
- 2) versus 3) : 37/49 versus 59/79, $\chi^2 = 0.01$, $p = 0.92$.
- 1) versus 2) : 77/83 versus 37/49, $\chi^2 = 6.40$, $p = 0.01$.

Table 2. Relationship between patient age and development of t-MDS or t-AML with different balanced chromosome aberrations.

Aberration	Age						
	0-9	10-19	20-39	40-59	60+	Unknown	Total
11q23	22	25	13	19	14	2	95
21q22	2	2	14	17	20	2	57
inv(16)		1	3	14	3	3	24
t(15;17)	3	2	15	11	13	1	45
t(9;22)	2	3	7	12	6	3	33
Others	9	6	21	39	78	15	168
Total	38	39	73	112	134	26	422

- 5) versus 6) : 47/93 versus 15/150, $\chi^2 = 47.53$, $p < 0.0000001$.
- 5) versus 7) : 47/93 versus 15/153, $\chi^2 = 48.77$, $p < 0.0000001$.
- 6) versus 7) : 15/150 versus 15/153, $\chi^2 = 0.02$, $p = 0.89$.

Table 3. Relationship between previous therapy with various DNA topoisomerase II inhibitors and development of t-MDS or t-AML with different balanced chromosome aberrations.

Aberrations	Type of DNA Topoisomerase II Inhibitor Previously Administered				Total
	Anthracyclines	Epipodophyllotox	Mitoxantrone	Dioxypip Deriv	
11q23	23	25	1		49
21q22	19	5	2	4	30
inv(16)	7		2	1	10
t(15;17)	9	5		9	23
t(9;22)	12	3	1		16
Others	20	4			24
Total	90	42	6	14	152

8) versus 9): 25/48 versus 17/84, $\chi^2 = 12.85$, $p = 0.0003$.
 10) versus 8) + 9): 9/23 versus 5/118, Fisher's exact test $p = 0.00002$.

aberrations: 17/84, had received epipodophyllotoxins ($p = 0.0003$). As far as patients with the t(15;17) are concerned, this aberration was observed in 9/14 patients treated with dioxypiperazine derivatives as compared to only 14/132 in patients treated with anthracyclines or epipodophyllotoxins ($p < 0.00002$).

Table 4 shows the relationship between age and previous therapy with various subtypes of DNA topoisomerase II inhibitor for all 152 patients with t-MDS and t-AML and any type of balanced chromosome aberration. If only the two major groups of patients previously treated with anthracyclines and epipodophyllotoxins are compared, 23/40 treated with epipodophyllotoxins were less than twenty years old as compared to only 12/89 less than twenty years of age in patients previously treated with anthracyclines ($p = 0.0000006$).

The complicated interrelationships between patient age, subtype of balanced chromosome aberration and previous chemotherapy with or without DNA topoisomerase II inhibitors, and with anthracyclines versus epipodophyllotoxins, were finally evaluated in multivariate analyses as shown on Tables 5 and 6. In this analysis previous therapy with DNA topoisomerase II inhibitors was still highly significantly related to development of t-MDS or t-AML with the characteristic balanced aberrations as compared to the uncharacteristic balanced aberrations. A significantly closer association was however observed for balanced translocations involving band 11q23 as compared to inv(16), t(15;17) and t(9;22) ($p = 0.024$) (Table 5). If age was taken into consideration there was no longer a significant association between previous therapy with epipodophyllotoxins and development of t-MDS or t-AML with translocations involving 11q23, or between previous therapy with anthracyclines and the development of t-MDS or t-AML with balanced translocations involving 21q22 ($p = 0.17$) (Table 6).

Table 4. Relationship between patient age and previous therapy with various DNA topoisomerase II inhibitors in patients with t-MDS or t-AML and balanced chromosome aberrations.

Age	Type of DNA Topoisomerase II Inhibitor Previously Administered				Total
	Anthracyclines	Epipodophyllotox	Mitoxantrone	Dioxypip Deriv	
0-9	7	7			24
10-19	5	6		2	13
20-39	24	7	1	7	39
40-59	33	7	2	4	46
60-	20	3	2	1	26
NR	2	1	1		4
Total	91	41	6	14	152

Abbreviation: NR, not reported.
 11) versus 12) : 23/35 versus 17/94, $\chi^2 = 24.86$, $p = 0.0000006$

Table 5. Relationship between age, previous chemotherapy with or without DNA topoisomerase inhibitors and development of t-MDS or t-AML with different balanced chromosome aberrations.

Age	Type of Chemotherapy	11q23	21q22	inv(16) t(15;17) t(9;22)	Others	Total
0-19	Alkyl alone	4	1	0	3	8
	ATTOP±Alkyl	41	3	10	6	60
20-	Alkyl alone	1	11	18	71	101
	ATTOP±Alkyl	35	34	45	29	143
Total		81	49	73	109	312

Multivariate analysis: t-MDS or t-AML with 11q23, 21q22, inv(16), t(15;17) and t(9;22) significantly related to previous therapy with ATTOP compared to other uncharacteristic balanced aberrations: $\chi^2 = 65.87$, $p < 0.0000001$
 11q23 in t-MDS or t-AML more closely related to previous therapy with ATTOP compared to 21q22, inv(16), t(15;17) and t(9;22) : $\chi^2 = 11.26$, $p = 0.024$

Discussion

The present study analyzing 422 published cases of t-MDS and t-AML with balanced chromosome aberrations demonstrates primarily that such cases have most often received chemotherapy for their primary tumor (Table 1). This confirms many previous investigations showing that the risk of t-MDS or t-AML predominantly is related to chemotherapy and not to radiotherapy. Furthermore, if compared to the group of patients with various uncharacteristic balanced aberrations, there is strong support for our previous suggestions that not only the balanced translocations involving chromosome bands 11q23 and 21q22,^{25,26} but also the inv(16), the t(15;17) and the t(9;22) in t-AML are often associated with previous therapy with DNA topoisomerase II inhibitors (Table 1). The figures for these three last-mentioned aberrations suggest that they are all, and to almost the same extent as the balanced translocations involving band 21q22, related to previous therapy

Table 6. Relationship between age, previous therapy with anthracyclines or epipodophyllotoxins and development of t-MDS or t-AML with different balanced chromosome aberrations.

Age	Type of ATTOP	11q23	21q22	inv(16) t(15;17) t(9;22)	Others	Total
0-19	Anthracycl.	6	2	3	1	12
	Epipodophyll.	17	0	4	3	24
20-	Anthracycl.	17	17	24	20	78
	Epipodophyll.	7	7	3	2	19
Total		47	26	34	26	133

Multivariate analysis: no significant associations between previous therapy with epipodophyllotoxins and development of t-MDS or t-AML with balanced translocations to band 11q23 or previous therapy with anthracyclines and development of t-MDS or t-AML with balanced translocations to band 21q22 $\chi^2 = 3.51$, $p = 0.17$ if patient age is included in the model.

with topoisomerase II inhibitors. However, the association is even closer for translocations involving band 11q23.

In t-MDS or t-AML, patients with balanced translocations involving band 11q23 are significantly more common below the age of 20 as compared to patients with all other balanced aberrations, which are most often observed in patients 20 years of age or older (Table 2). This confirms the general experience from pediatric hematology. As far as the subtypes of DNA topoisomerase II inhibitor are concerned, the univariate analysis suggests that the balanced translocations involving band 11q23 in t-MDS or t-AML are associated with previous therapy with epipodophyllotoxins whereas the other balanced aberrations are associated with previous therapy with anthracyclines (Table 3). The t(15;17) is significantly more frequent in t-AML following therapy with the dioxypiperazine derivatives as compared to therapy with the anthracyclines and the epipodophyllotoxins. These three apparent drug-related correlations, however, are complicated by an uneven distribution of age and race. Thus, patients previously treated with epipodophyllotoxins are generally younger as compared to patients treated with anthracyclines (Table 4), most likely reflecting an increased use of the epipodophyllotoxins in pediatric oncology in recent years versus a more widespread use of the anthracyclines in adults. As far as the t(15;17) is concerned there could either be an association to previous therapy with dioxypiperazine derivatives, or alternatively an ethnical explanation, since all these patients were Chinese.

If introducing the data in a multivariate analysis, the association between previous therapy with epipodophyllotoxins and development of t-MDS or t-AML with balanced translocations involving band 11q23, and the association between previous therapy with anthracyclines and the development of the other characteristic balanced aberrations, although highly significant in the univariate analyses, are no

longer significant ($p = 0.17$) (Table 6). Thus, younger age and not type of DNA topoisomerase II inhibitor seems to predispose to development of t-MDS or t-AML with translocations involving chromosome band 11q23. As far as the predominance of t-AML with t(15;17) in patients treated with dioxypiperazine derivatives is concerned, this association could be drug-related, although based on the well described geographic heterogeneity of chromosome aberrations in AML,²⁹ geographic or ethnical differences might be a more likely explanation.

The multivariate analysis furthermore confirms the highly significant association between previous therapy with the DNA topoisomerase II inhibitors and the development of t-MDS or t-AML with the characteristic balanced chromosome aberrations, as compared to the uncharacteristic balanced aberrations ($p < 0.000001$) (Table 5). Furthermore, the even closer association between previous therapy with DNA topoisomerase II inhibitors and development of t-MDS or t-AML with translocations involving chromosome band 11q23, as compared to the other 4 types of characteristic balanced aberration, is confirmed.

Future studies after accumulation of more cases of t-MDS and t-AML may confirm our results, and may allow new comparisons. If combined with experimental studies the results may lead to a better understanding of the mechanisms for the development of the unbalanced and the balanced chromosome aberrations in malignancy.

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MKA and JP-B have designed the study. MKA, BJ and SOL executed the study, and all authors participated in the evaluation of the results and in writing the paper. MKA, as the principal investigator, is the first author. BJ and SOL, as second and third author, have made major contributions, and JP-B is the senior investigator.

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Disclosures

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