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Therapy-related acute lymphoblastic leukaemia with *MLL* rearrangements following DNA topoisomerase II inhibitors, an increasing problem: report on two new cases and review of the literature since 1992

METTE KLARSKOV ANDERSEN,[1] DEBES H. CHRISTIANSEN,[1] BJARNE ANKER JENSEN,[2] PETER ERNST,[3] GUNNAR HAUGE[4] AND JENS PEDERSEN-BJERGAARD[1] [1]*Cytogenetic Laboratory, Section of Haematology/Oncology, Department of Clinical Genetics, Rigshospitalet, Copenhagen,* [2]*Department of Internal Medicine F, Section of Haematology, Hillerød Hospital, Denmark, and* [3]*Department of Haematology and* [4]*Department of Medical Cytogenetics, Haukeland Sykehus, Bergen, Norway*

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Summary. A highly increased risk of myelodysplasia (MDS) and acute myeloid leukaemia (AML) is well established in patients previously treated for other malignancies with alkylating agents or topoisomerase II inhibitors. More recently, single cases of acute lymphoblastic leukaemia (ALL), often presenting balanced translocations involving chromosome band 11q23, have been observed. We present two such cases with t(4;11)(q21;q23), one of whom had previously received only single-agent chemotherapy with 4-epi-doxorubicin. A review of the literature since 1992 including these two patients reveals a total of 23 cases of ALL or lymphoblastic lymphoma after chemotherapy presenting balanced translocations to 11q23. All 23 patients had previously received at least one topoisomerase II inhibitor, and in two patients 4-epi-doxorubicin had been administered as single-agent chemotherapy for breast cancer. The latency period to development of t-ALL was 24 months or less in 20 out of 22 cases. The *MLL* gene was found to be rearranged in 14 out of 14 cases, and in three out of six cases the breakpoint was at the telomeric part of the gene, as observed in most cases of AML following therapy with topoisomerase II inhibitors. These results indicate that patients with ALL and balanced translocations to chromosome band 11q23 following chemotherapy with topoisomerase II inhibitors in the future should be included with cases of MDS or AML in calculations of risk of leukaemia.

Keywords: therapy-related ALL, DNA topoisomerase II inhibitors, chromosome band 11q23, rearrangement of MLL.

Acute myeloid leukaemia (AML), often presenting as myelodysplastic syndrome (MDS), has been shown to occur with a highly increased frequency in studies of patients treated intensively with alkylating agents or topoisomerase II inhibitors (Park & Koeffler, 1996; Van Leuwen, 1996;), but an increased risk of acute lymphoblastic leukaemia (ALL) or of chronic leukaemias has never been demonstrated.

During the last decade, however, an increasing awareness has emerged of the occurrence of single cases of ALL in patients previously treated with chemotherapy (Hunger *et al*, 1992). A 1992 review disclosed less than 30 cases of therapy-related ALL (t-ALL) published in the literature with detailed information on previous therapies and cytogenetic data (Pedersen-Bjergaard, 1992). Surprisingly, as many as 10 of these patients presented a t(4;11)(q21;q23) and all had previously received therapy with DNA topoisomerase II inhibitors. The association was simultaneously emphasized by two other reports (Auxenfants *et al*, 1992; Pui, 1992). As therapy-related AML (t-AML) with balanced translocations to 11q23 and chimaeric rearrangements of the *MLL* gene is strongly associated with previous therapy with topoisomerase II inhibitors (Pui, 2000), it seems very likely that cases of t-ALL with t(4;11)(q21;q23) and other balanced translocations to 11q23 could also result from treatment with topoisomerase II inhibitors.

Correspondence: M. K. Andersen, M.D., The Cytogenetic Laboratory Section 4052, Department of Clinical Genetics, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark. E-mail: MKA@rh.dk

We have recently observed two cases of t-ALL with t(4;11)(q21;q23), one of which occurred after single-agent chemotherapy with 4-epi-doxorubicin. A follow-up review of the literature since 1992 has been performed to further explore a possible causal relationship between chemotherapy with topoisomerase II inhibitors and subsequent development of ALL with balanced translocations to chromosome band 11q23.

PATIENTS AND METHODS

Patient 1. A 52-year-old woman presented with breast cancer in 1989. She underwent surgery and did not receive any adjuvant chemotherapy. In 1998 metastases to the ribs and lumbar spine were diagnosed, and she was treated with radiotherapy, 8 Gy as a single fraction towards TH XII–LIII. Subsequently, she received tamoxifen 30 mg/d for 6 months until the disease progressed. From January to August 1999 she received single-agent chemotherapy with 10 courses of 4-epi-doxorubicin, administered as 170 mg every third week with adjustment of dose according to cytopenia. The cumulative dose of 4-epi-doxorubicin was 1620 mg. In October 1999 the patient presented with fever over the previous 2–3 weeks, night sweats, fatigue and bruising. She was moderately anaemic (haemoglobin 9·3 g/dl) and thrombocytopenic (platelet count 77×10^9/l), lactate dehydrogenase (LDH) was $> 2{\cdot}000$ U/l and her leucocyte count was 616×10^9/l with 87% lymphoblasts. A bone marrow aspirate was hypercellular with 82% lymphoblasts. The immunophenotype was CD19, TdT and CD22 positive, faintly CD34 positive and CD10 negative, characteristic for pro-B ALL.

The patient was treated with vincristine, prednisolone, cyclophosphamide and mitoxantrone, but obtained only a partial response. She refused further intensive chemotherapy and is now followed on maintenance chemotherapy with methotrexate, 6-mercaptopurine and prednisolone.

Patient 2. A 25-year-old man presented in 1998 with testicular cancer (seminoma) and metastases to the right inguinal lymph nodes. He was treated with surgery followed by radiotherapy, 25·2 Gy towards a para-aortic and inguinal field. Five months later, a relapse at the inguinal lymph nodes was diagnosed. Between March and May 1999 the patient obtained a complete remission after three courses of cisplatin, etoposide and bleomycin. The cumulative dose of cisplatin was 565 mg, etoposide was 2835 mg and bleomycin was 270 i.e. In May 2000 routine laboratory tests showed a leucocyte count of 114×10^9/l, with a normal haemoglobin level and platelet count. The physical examination was normal, but a bone marrow aspirate showed hypercellularity with 88% lymphoblasts. Immunophenotyping was CD19 and CD22 positive, faintly CD34 positive and CD10 negative, indicating a pro-B ALL.

Intensive chemotherapy with vincristine, prednisolone, daunorubicin, L-asparaginase and intrathecally administered methotrexate resulted in complete remission, and the patient is now receiving consolidation chemotherapy.

Cytogenetics and fluorescence in situ hybridization (FISH). Conventional karyotyping (G-banding) was performed on bone marrow aspirates at time of diagnosis of ALL in both patients. The karyotype of case 1 was 46,XX, t(4;11)(q21;q23)[11]/47,XX, +X,t(4;11)[7]/46,XX[8], and that of case 2 was 46,XY,t(4;11)(q21;q23)[12].

FISH was performed as recommended by the manufacturers on metaphase chromosomes with a dual-colour MLL probe (Vysis, Downers Grove, IL, USA) in patient 1 and with an MLL probe (Oncor, Gaithersburg, MD, USA) in patient 2. In both cases, FISH analysis confirmed a t(4;11)(q21;q23) with split signals of MLL.

MLL-AF4 reverse transcription-polymerase chain reaction (RT-PCR) amplification and sequencing. Total RNA was extracted from bone marrow cells with the TRIzol reagent (Gibco Life Technologies, Grand Island, NY, USA). First-strand cDNA synthesis of 1 μg of total RNA was performed with the Superscript II RNase H^- Reverse Transcriptase kit (Gibco Life Technologies). PCR was performed in a total volume of 20 μl containing 0·5 μl of the cDNA solution, PCR buffer (Qiagen, Hilden, Germany), 0·1 mmol/l dNTP (Pharmacia Biotech, Uppsala, Sweden), 10 μmol/l of primers MLL-5·1 and AF4·1 (DNA Technology, Aarhus, Denmark) and 0·5 U of HotStarTaq DNA polymerase (Qiagen). Cycle conditions were as follows: initial denaturation at 95°C for 15 min, followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 60°C for 1 min, and extension at 72°C for 1 min. The primer sequences were: MLL-5·1 (sense), 5′-GGAAGTCAAGCAAGC AGGTC-3′ and AF4·1 (antisense), 5′-TGAGCTGAAGCTGGT CTTCGAGC-3′. The *MLL*/*AF4* fusion PCR products were sequenced using the ABI PRISM Dye Terminator Cycle Sequencing kit (Perkin Elmer). In both cases a rearrangement of *MLL* and *AF4* was observed. In patient 1 the breakpoint of *MLL* was localized within intron 8, whereas in patient 2 it was localized more centromeric within intron 6. Exon/intron nomenclature is according to Gu *et al* (1994).

REVIEW OF THE LITERATURE SINCE 1992

This review is based on data from Felix Mitelman's Catalogue on Chromosome Aberrations in Cancer (Mitelman, 1998), our own search of the literature and the two new cases presented. Since 1992 a total of 22 cases of t-ALL and one case of therapy-related lymphoblastic lymphoma with balanced chromosome aberrations involving chromosome band 11q23 have been reported (Auxenfants *et al*, 1992; Kobayashi *et al*, 1993; Jonveaux *et al*, 1994; Narayanan *et al*, 1994; Domer *et al*, 1995; Felix *et al*, 1995; Imashuku *et al*, 1996; Zhang *et al*, 1996; Megonigal *et al*, 1997; Nasr *et al*, 1997; Rowley *et al*, 1997; Laughlin *et al*, 1998; Pinto *et al*, 1998; Secker-Walker *et al*, 1998; Bigoni *et al*, 1999; Thandla *et al*, 1999) (Table I).

Twelve patients were female and 11 were male, aged 2–64 years (median 35). Six out of the 23 patients (26%) were younger than 15 years of age. The primary tumour was breast cancer in seven patients, testicular cancer, lymphomas and sarcomas in three patients each, and various other malignancies in six patients. The latency period to development of t-ALL was 9–48 months (median 19), and 24 months or less in 20 out of 22 cases.

Table I. Acute lymphoblastic leukaemia or lymphoblastic lymphoma with balanced translocations to band 11q23 following chemotherapy, reported since 1992.

Reference (case no.)	Age (years) /sex	Primary malignancy	Previous treatment	Latent period (months)	FAB class/ cytogenetics/*MLL* status
Auxenfants *et al* (1992) (1)	56/Female	Breast cancer	Ctx + Mit + 5FU + RT	9	L1/t(4;11)
Auxenfants *et al* (1992) (2)	60/Male	Small cell lung cancer	Dox + Ctx + VCR+ Etop + RT	21	L2/t(4;11),i(7q)
Kobayashi *et al* (1993)	44/Female	Breast cancer	Flu + Pirub.	19	B-cell L1*/t(11;19)/ *MLL* rearr.
Joveneaux *et al* (1994)	35/Male	AML M5 t(6;11) *MLL* rearr. intron 7	DNR + AraC + Mit + M-Amsa	12	B-cell/t(4;11)/ *MLL* rearr. intron 9
Narayanan *et al* (1994) (2)	36/Female	Hodgkin	Clb + Vlb + Pro+ Pred + Dox + Etop + VCR + RT	24	Pre-pre B ALL/t(4;11)
Narayanan *et al* (1994) (3)	28/Male	Hodgkin	Me + Vlb + Pro + Pred + Clb + Dox + Etop	36	Pre B/t(4;11)
Felix *et al* (1995) (8)	9/Female	Non-Hodgkin	Ctx + DNR + VCR + Pred + l-Asp + Mtx	20	T-ALL/ del(6q), +8,del(11)(q23)/ 2*MLL* rearr.
Felix *et al* (1995) (10)	10/Male	Osteogenic sarcoma	Dox + Carbo + Ifos+ Mtx + Etop + VCR	16	L1/t(4;11)/ *MLL* rearr.
Domer *et al* (1995) (12)	5/Male	Neuroblastoma	Cis + Etop + Dox + Ctx	18	L1/t(4;11)/ *MLL* rearr. intron 8
Zhang *et al* (1996) (3)	64/Female	Breast cancer	Epi	19	Pre B-ALL/+X, t(4;11),i(17q)/ *MLL* rearr.
Imashuku *et al* (1996) (2)	2/Male	Neuroblastoma	Ctx + VCR + Dox + Etop + Cis	22	L1/t(5;11)(q35;q23)/ *MLL* rearr.
Nasr *et al* (1997)	36/Female	Breast cancer	Dox + 5FU + Ctx+ Ellip + Etop + Tax + RT	?	Pre B-ALL/t(4;11)/ *MLL* rearr.
Rowley *et al* (1997) (10)	NS/Male	T-ALL (normal karyotype)	Teni + Dox	21	B-ALL/t(5;8)(q33;q12) t(11;16)(q23;p13)/ *MLL* rearr.
Megonigal *et al* (1997)	33/Female	Rhabdomyo-sarcoma	Etop + Ctx + Ifos + Dact + VCR + RT	15	L1/t(4;11)/ *MLL* rearr. intron 6
Secker-Walker *et al* (1998) (111)	45/Female	Breast cancer	Mit + Alkyl + Pred + RT	12	Pre B-ALL/t(4;11), del(17)(p11)
Secker-Walker *et al* (1998) (311)	31/Male	Testicular cancer	Etop + Cis + Bleo	24	ALL/t(4;11)
Secker-Walker *et al* (1998) (430)	41/Male	Testicular cancer	Etop + Cis	16	Pre B-ALL/t(4;11)
Laughlin *et al* (1998) (5)	35/Female	Breast cancer	Dox + 5FU + Mtx + Ctx + Cis + BCNU + ABMT	13	L1/t(1;11)(p32;q23)
Pinto *et al* (1998)	13/Female	Osteogenic sarcoma	Cis + Dox	22	L2/t(1;11)(p32;q23)
Bigoni *et al* (1999)	42/Female	Uterine cancer	Etop + Epi + Carbo + RT	12	Pre B-ALL L2/t(3;6)(p21:q21),del(3)(p24), t(4;11), del(6)(q15), iso(7)(q10),add(9)(p22), del(17)(p11)/ *MLL* rearr. intron 6
Thandla *et al* (1999)	10/Male	Hepatocellular carcinoma	Dox + Cis + Etop + Carbo + Ifos	48	lymphobl. lymphoma/t(1;13)(q4;q13),t(11;19) +X, +5, +8, +13, +14/*MLL* rearr.
Present study	64/Female	Breast cancer	Epi + RT	10	Pre B-ALL/t(4;11)/ *MLL* rearr. intron 8
Present study	27/Male	Testicular cancer	Etop + Cis + Bleo + RT	18	Pre B-ALL/t(4;11)/*MLL* rearr. intron 6

*Denotes cytogenetics not performed.

Ctx, cyclophosphamide; Mit, mitoxantrone; 5FU, fluorouracil; RT, radiotherapy; Dox, doxorubicin; VCR, vincristine; Etop, etoposide; Flu, fludarabine; Pirub, pirarubicin; DNR, daunorubicin; AraC, cytosine arabinoside; Mit, mitoxantrone; M-Amsa, amsacrine; Clb, chlorambucil; Vlb, vinblastine; Pro, procarbazine; Pred, prednisone; Me, mechlorethamine; l-Asp, l-asparaginase; Mtx, methotrexate; Carbo, carboplatin; Ifos, ifosfamide; Epi, 4-epi-doxorubicin; Ellip, ellipticin; Tax, taxol; Cis, cisplatin; Bleo, bleomycin; BCNU, carmustine; ABMT, autologous bone marrow transplantation; Teni, teniposide; Dact, dactinomycin; Alkyl, alkylating agent not otherwise specified.

All 23 patients had previously received at least one topoisomerase II inhibitor. Thus, 12 patients had received etoposide, 11 patients doxorubicin, three patients mitoxantrone, another three patients 4-epi-doxorubicin and four patients received other topoisomerase II inhibitors. Thirteen patients had also received classic alkylating agents and 10 patients received platinum derivatives, in all cases combined with topoisomerase II inhibitors. Two patients, including case 1 in the present study, had received single-agent chemotherapy with 4-epi-doxorubicin, and another patient had received two different topoisomerase II inhibitors only. Two patients had received topoisomerase II inhibitors in combination with other cytostatic agents not previously demonstrated as leukaemogenic.

Sixteen patients with t-ALL presented a t(4;11)(q21;q23), two presented a t(1;11)(p32;q23), another two a t(11;19)(q23;p13) and, finally, a t(5;11)(q35;q23), a t(11;16)(q23;p13), and a del(11)(q23) were each observed in one patient.

Data on response to ALL therapy were reported in 15 out of the 23 patients. Of these 15 patients, nine obtained a complete remission, whereas the remaining six patients did not respond to intensive chemotherapy. The follow-up periods were in most cases short and so it was not possible to assess remission duration or survival.

In 14 out of 14 cases studied an *MLL* gene rearrangement was demonstrated, and in three out of six of these cases the breakpoints were localized at the telomeric part of the gene within introns 8, 8 and 9, respectively, whereas in the other three cases the breakpoints were at the centromeric part of the gene within intron 6. Exon/intron nomenclature is according to Gu *et al* (1994).

DISCUSSION

All 10 cases of t-ALL with t(4;11) following chemotherapy published up to 1992 (Pedersen-Bjergaard, 1992), as well as all 23 cases of t-ALL with balanced translocations to chromosome band 11q23 following chemotherapy published since 1992, had received at least one topoisomerase II inhibitor. This fact strongly supports a causal relationship between chemotherapy with topoisomerase II inhibitors and subsequent development of t-ALL. Although an increasing awareness of a possible association may have resulted in a selection for publication of cases demonstrating this association, three additional observations support a causal relationship. First, three patients in the updated series had received topoisomerase II inhibitors only, and two patients had received a topoisomerase II inhibitor combined with cytostatic agents not previously verified as leukaemogenic. Second, the breakpoints in three out of six cases analysed so far were localized at the telomeric part of the gene within introns 8–9 characteristically rearranged in t-AML following chemotherapy with topoisomerase II inhibitors, as well as in infant leukaemia with translocations to 11q23 (Broeker *et al*, 1996; Cimino *et al*, 1997). Third, the short latency period to development of t-ALL of 24 months or less in 20 out of 22 cases, which is similar to that observed in t-AML after previous therapy with topoisomerase II inhibitors (Pedersen-Bjergaard *et al*, 1993).

The relatively high number of patients younger than 15 years of age reported with t-ALL and balanced translocations to 11q23 is in accordance with our previous observations. Thus, in a review of the literature of t-AML with various recurrent balanced translocations, 11q23 aberrations were significantly related to young age compared with other recurrent balanced translocations (Andersen *et al*, 1998).

In conclusion, it seems justified in risk calculations of therapy-related leukaemia to include cases of t-ALL with balanced translocations to chromosome band 11q23 in addition to cases of t-AML. Furthermore, new cases of t-ALL may provide further information on the molecular biology of therapy-related leukaemia, on its association with specific types of previous therapy and, particularly, on questions related to differences in the phenotype of the leukaemic cell.

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