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Case Report

THERAPY RELATED ACUTE MYELOID LEUKEMIA IN A CHILD- A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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ABSTRACT

Therapy related myelodysplasia /acute myeloid leukemia (t-MDS/AML), a well-known complication is caused by alkylating agents, radiation and topoisomerase II inhibitors, the primary tumours being leukemias, lymphomas and sarcomas. A 9 year old female child with prior history of surgically removed sacrococcygeal tumour 3 years back was admitted with bilateral pelvic mass. The excised tumour was diagnosed as embryonal tumour, a subtype of primitive neuro ectodermal tumour based on histology and immunohistochemistry. Three years after completion of 14 cycles of intensive chemotherapy, bone marrow studies showed 40% blasts with characteristics of acute myeloid leukemia M0 type. By flowcytometry the CD45 cell clusters were positive for CD13, CD33, HLA DR, and CD117. Cytogenetics revealed MLL gene rearrangement. Therapy related AML-M0 with MLL rearrangement secondary to PNET is very rare. Patients treated with chemotherapy should be followed up vigilantly to recognize therapy related leukemic events.

Keywords: *Therapy related AML, PNET, Chemotherapy*

INTRODUCTION

Therapy related myeloid neoplasms (t-MN), commonly known as myelodysplasia/acute myeloid leukemia (t-MDS/AML), is a well-known complication after radiotherapy and chemotherapy. Chemotherapeutic drugs known to cause second malignancy are alkylating agents and topoisomerase II inhibitors (Bhatia *et al.,* 2002). The primary malignant disorders for which treatment had been given could be acute lymphoblastic leukemia, NonHodgkin lymphoma, Hodgkin lymphoma, ovarian malignancy, breast carcinoma and sarcomas(Bloomsfield *et al.,* 2002; H-F Tien *et al.,* 2000; Jolanta *et al.,* 2005; Krishnan *et al.,*2000; Pui C-H *et al.,*1991 and Smita Bhatia *et al.,* 2007). A single cohort study on Ewing's sarcoma and primitive neuroectodermal tumour of bone, found statistically significant t-MDS/AML occurrence when treatment is intensified (Smita Bhatia, 2013). We present a case report of t AML in a child for whom chemotherapy was given for primitive neuroectodermal tumour.

CASE

A 6-year-old female child had been evaluated for constipation and left lower limb weakness. She was diagnosed with sacrococcygeal tumour and surgical excision was done elsewhere. As per the patient's records, postsurgical chemotherapy or radiotherapy was not given. Details of biopsy were also not available. Three years later, at 9 years of age, she developed bilateral mass in the pelvic region. Magnetic resonance imaging revealed well defined hyperintense and hypointense lesion with enhancing walls and multiple internal septations in S2-S4 region. Mass excision of the tumour was done. Grossly, the tumour was 5x 4.5 x2.5 cm grey white to grey brown soft tissue mass, with the cut surface showing cystic areas. Microscopically, predominant fibro-collagenous tissue was seen, with fragments of tumour made up of small blue cells with true rosettes. By immunohistochemistry, the tumour cells were positive for vimentin and cytokeratin and focally positive for S100 and CD99. KI labelling was 60 %. (Figures 1a, b, c, d). They were negative for glial fibrillary acid protein, epithelial membrane antigen, synaptophysin and chromogranin. Due to the above said features, diagnosis was concluded as embryonal tumour, a subtype of primitive neuro ectodermal tumour. Bone marrow biopsy done for staging was free of tumour cells.

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Postsurgical chemotherapy was started after two months. Fourteen cycles of chemotherapy were given with cumulative doses of vincristine 14mg/m^2, cyclophosphamide 8.4g/m^2, doxorubicin 375mg/m^2, ifosfamide 12.6g/m^2 and etoposide 0.7g/m^2. The patient was on regular follow up with no untoward symptoms, signs or laboratory values.

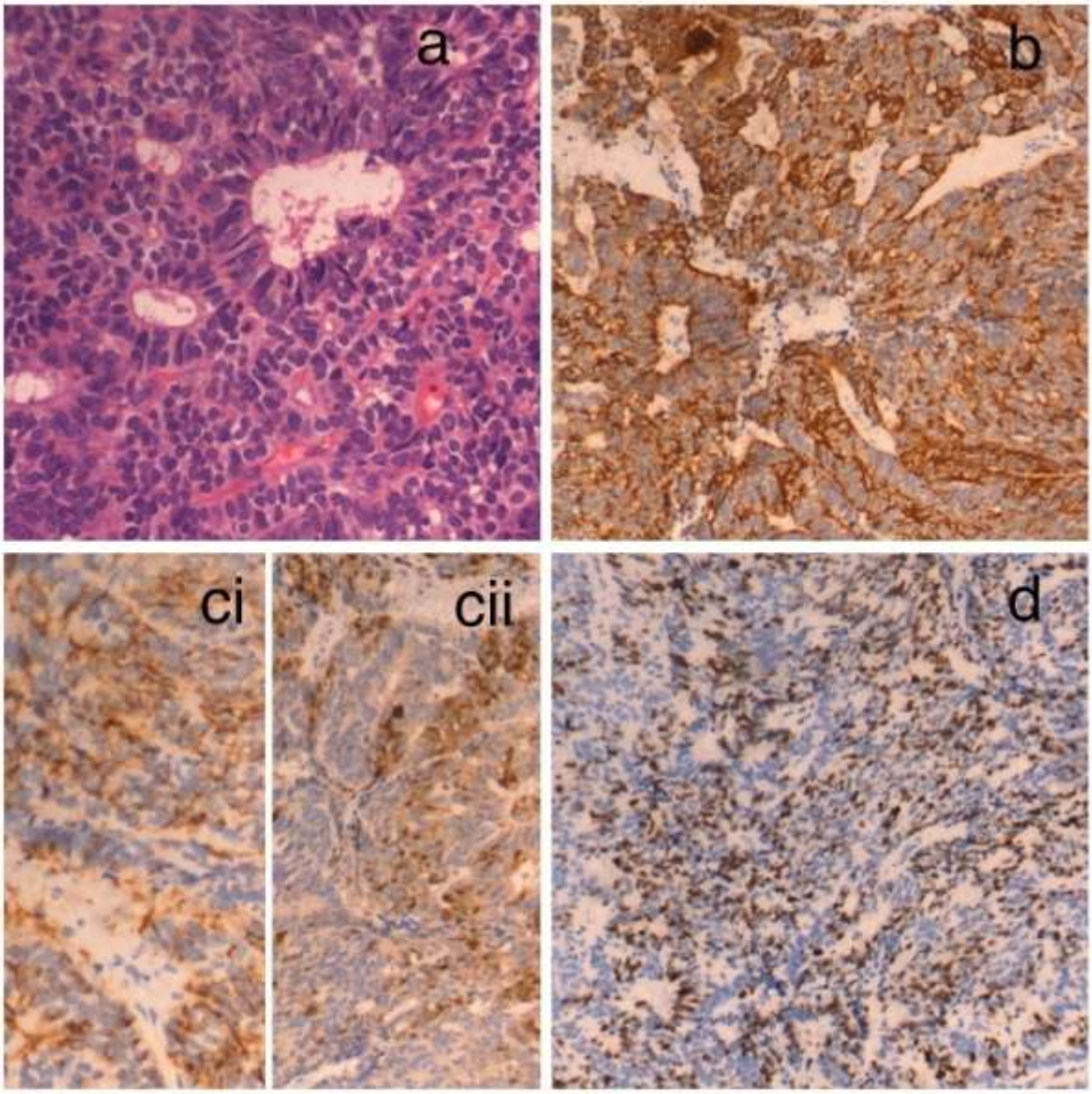

Figure 1a: Haematoxylin and Eosin, 40X Figure1b-1d: Immunohistochemistry Figure1b: Cytokeratin Figure:1ci S100 Figure1cii: CD99 Figure1d: Ki labeling of tumour sections

At 12 years of age that is, three years after completion of chemotherapy, she presented with easy fatigability and loss of appetite. There was no symptom involving fever, bony pain, weight loss and mucosal bleed. Routine hematologic investigations showed RBC count 1.05 million/cu mm, hemoglobin 4 grams/dl, MCV 110 fl, total leukocyte count 3200 cells/cu mm and platelet count 1.51 cells/ cu mm. Peripheral smear showed macrocytic anaemia. The patient was transfused with one unit of packed red blood cells. Inj. Vitamin B12 and folic acid were also given. As there was no clinical and hematologic response, bone marrow studies were performed after a month. The bone marrow aspirate showed 40%

blasts with characteristics of acute myeloid leukemia M0 type (Figure 2a-c). By flow cytometry, CD45 cell clusters were 90.9% positive for CD13 with moderate intensity, 89.6% positive for CD33 with moderate intensity, 86.5% positive for HLA DR with moderate intensity and 28.5% positive for CD117. T and B cell markers were negative. Bone marrow biopsy showed a hypocellular marrow with cellular areas showing immature myeloid cells (Figure 2d). Cytogenetics revealed a female karyotype with derivative chromosome 11, with translocation involving chromosome 11 and 23, that is mixed lineage leukemia gene (MLL) (Figure 3). Fluorescent *in situ* hybridization (FISH) with MLL break apart probe was not done due to economic constraints. The patient was not followed up further since the parents wished to seek non allopathy treatment.

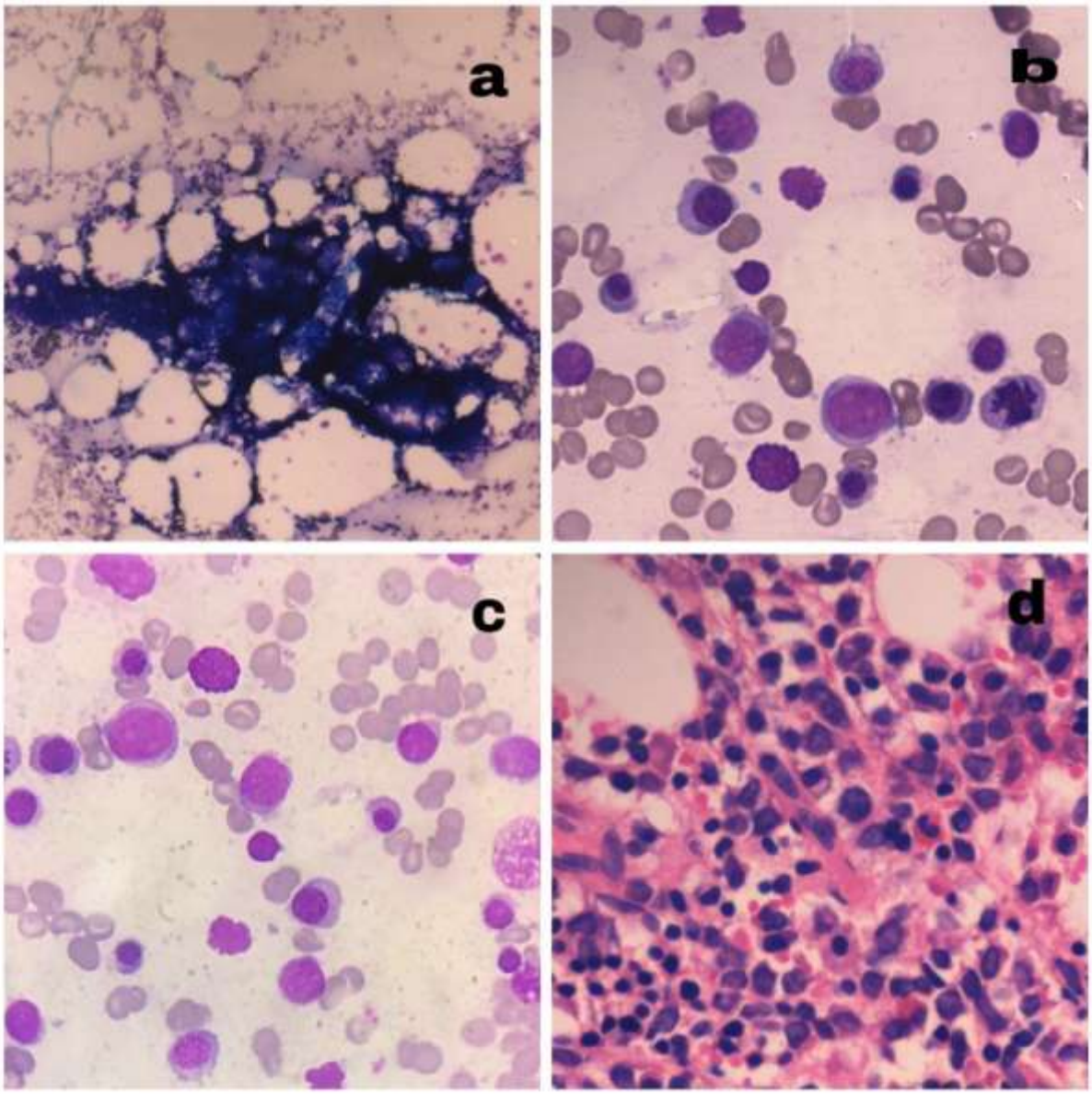

Figure 2a: Bone marrow aspirate (Leishman stain, 10X) Figure 2b: Bone marrow aspirate (Leishman stain, 40X) Figure 2c: Bone marrow aspirate (Leishman stain,100X) Figure 2d: Bone marrow biopsy (Haematoxylin and Eosin stain, 40X)

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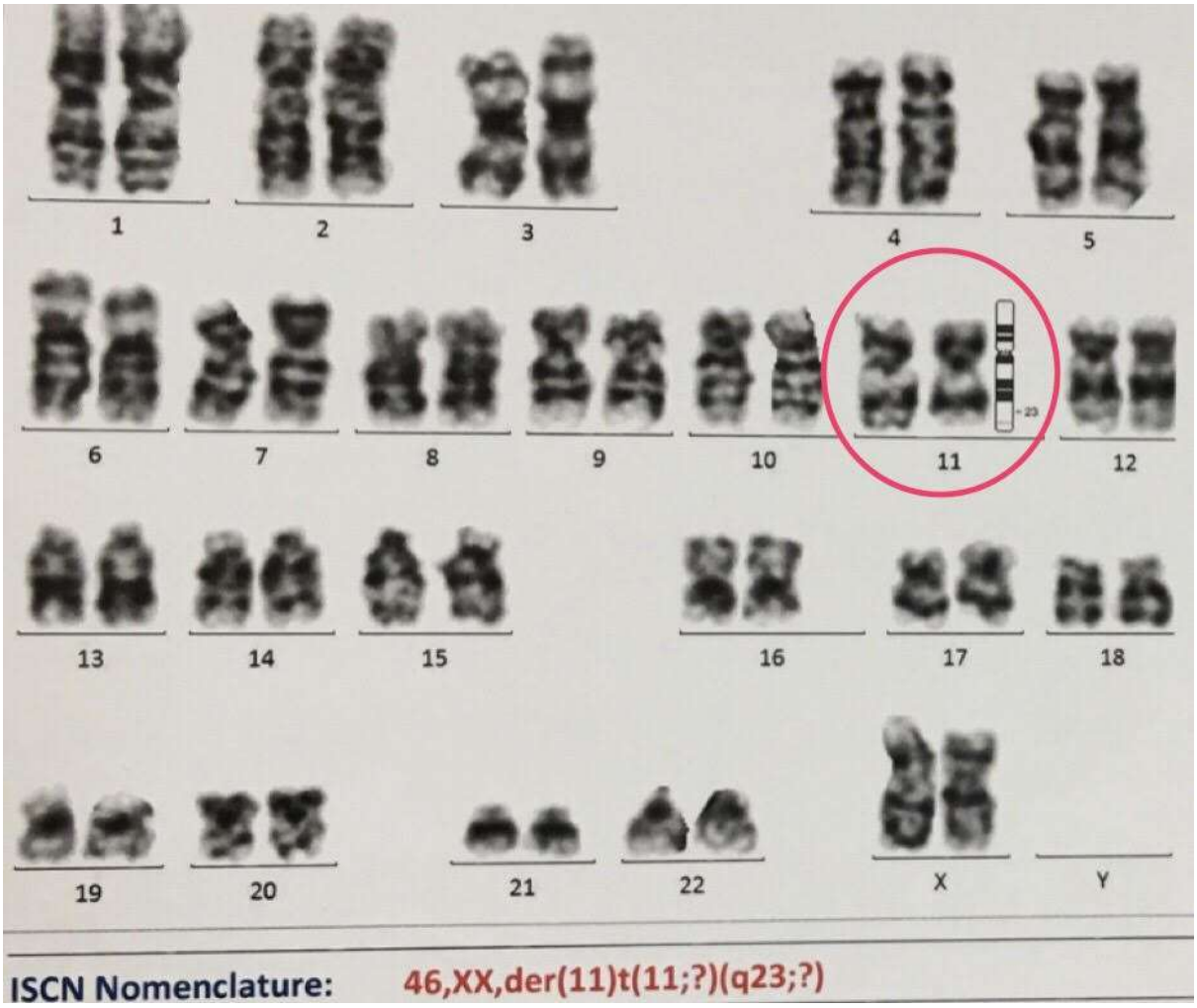

Figure 3: Karyotyping showing translocation of chromosomes 11 and 23

DISCUSSION

Chemotherapy and radiotherapy are known to cause chromosomal double strand breaks. These breaks are repaired by nonhomologous recombination or nonhomologous end joining (NHEJ) repair mechanisms which, when deranged, are associated with chromosomal translocations. It has been observed that 1% to 15% of patients who undergo chemotherapy with anticancer regimens develop therapy related leukemias (Smith RE *et al.*,2003).But a cohort study of 578 children who underwent chemotherapy for Ewing's sarcoma/PNET had occurrence of 0.02% t MDS/AML only (Smita Bhatia, 2013). Alkylating agents and topoisomerase II inhibitors are known to cause t MDS/AML. When the dose of the three drugs, doxorubicin, cyclophosphamide, ifosfamide, was higher, it was observed that there is statistically significant increase in leukemic development. The combination of ifosfamide 140gm/m^2 ,with cyclophosphamide at 17.6gm/m^2 and doxorubicin at 456mg/m^2,increased the risk of t MDS/AML as compared to lower doses in a regimen which included vincristine and etoposide also. But in our case, cumulative doses of the drugs were much lower - ifosfamide 12.6 g/m^2, cyclophosphamide 8.4 g/m^2, doxorubicin 375 mg/m^2, in addition to vincristine and etoposide, since the chemotherapy was postsurgical. This indicates individual variability in the development of t MDS/AML due to genetic susceptibility to toxic exposures.

Rearrangements of the MLL gene on chromosome band of 11q23 is known to be caused by alkylating agents/radiation and topoisomerase II inhibitors (Travis *et al.*, 2000).The activation of xenobiotic substrates of the drugs by cytochrome P450 (CYP) enzymes cause highly reactive electrophilic intermediates that can damage DNA(Travis *et al.*, 2000). In our patient, the usage of alkylating agent cyclophosphamide and topoisomerase II inhibitors ifosfamide and doxorubicin might have caused MLL rearrangements resulting in t-AML. This is a rare event because no case report of t AML with MLL rearrangement secondary to PNET is available in literature though a cohort of 578 patients of Ewing's, PNET had 11 t AML (1.9 %) and only 3 (0.5 %) of them had 11q23 abnormality. Our patient presented with cytopenias and overt AML without preceding myelodysplastic phase. Smita Bhatia stated in her manuscript that patients who had topoisomerase II inhibitors often present with overt AML but with prominent monocytic component (Travis *et al.*, 2000; Travis *et al.*, 1999). But our case had morphologic and immunophenotypic characters of AML- M0 in a cytopenia and aleukemic background. There was no co-expression of lymphoid associated antigens on leukemic blasts. Tien *et al*. (2000) also observed the absence of lymphoid associated antigens in de novo AML with MLL rearrangements (Van Leewen *et al.*, 1994).Though peripheral blood was aleukemic, timely performance of bone marrow in unresponsive anaemia, and clinical and morphologic recognition helped to detect the leukemic event. Even mild chemotherapeutic regimens cause gene rearrangement and secondary malignancy in a genetically susceptible individual.

CONCLUSION

Therapy related AML with MLL rearrangement secondary to PNET is a very rare event. Combination of alkylating agent cyclophosphamide and topoisomerase II inhibitors doxorubicin, ifosfamide might be the causative agents for DNA damage. Patients who are on chemotherapeutic agents should be on vigilant clinical and hematologic follow up to recognize therapy related leukemic events. Bone marrow studies are indicated in patients with unresponsive anaemia and untoward clinical symptoms.

REFERENCES

Bhatia S, Sather HN, Pabustan O, Gaynon P, Trigg M, Robison LL(2002). Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukemia after 1983. *Blood* **99** 4257-4264

Bloomsfield CD, Archer KJ, Mrozek K, *et al.*, (2002). 11q23 balanced chromosome aberrations in treatment related myelodysplastic syndromes and acute leukemia: report from an international workshop. *Genes Chromosomes Cancer* **33** 362-378

H-F Tien, C-H Hsiao, J-L Tang, W Tsay, C-H Hu, Y-Y Kuo, C-H Wang, Y-C Chen, M-C Shen, D-T lin(2000). Characterization of acute myeloid leukemia with MLL rearrangements- no increase in the incidence of coexpression of lymphoid- associated antigens on leukemic blasts. *Leukemia* **14** 1025-1030.

Jolanta Libura, Diana J. Slater, Carolyn A. Felix, and Christine Richardson (2005). Therapy-related acute myeloid leukemia- like MLL rearrangements are induced by etoposide in primary human CD 34^{+} cells and remain stable after clonal expansion. *Blood* **105** 2124-2131

Krishnan A, Bhatia S, Slovak ML, *et al.*, (2000). Predictors of therapy related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. *Blood* **95** 1588-93.

Pui C-H, Ribiero RC, Hancock ML, *et al.*, (1991). Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *New England Journal of Medicine* **325** 1682-1687

Smita Bhatia, Mark D. Krailo, Zhengjia Chen, Laura Burden, Frederic B. Askin, Paul S. Dickman, Holcombe E. Grier, Michael P. Link, Paul A. Meyers, Elizabeth J. Perlman, Aaron R. Rausen, Leslie L. Robison, Teresa J. Vietti and James S. Miser (2007). Therapy related myelodysplasia and acute myeloid leukemia after Ewing sarcoma and primitive neuroectodermal tumor of bone: a report from the Children's oncology group. *Blood* **109** 46-51

Smita Bhatia (2013). Therapy related myelodysplasia and acute myeloid leukaemia. *Seminars in Oncology* **40** 1-14

Smith RE, Bryant J, Decillis A and Anderson S (2003). Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: The National Surgical Adjuvant Breast and Bowel Project Experience. . *Journal of Clinical Oncology* **21** 1195- 1204

Travis LB, Andersson M, Gospodarowicz M, *et al.*, (2000). Treatment –associated leukemia following testicular cancer. *Journal of the National Cancer Institute* **92** 1165-1171

Travis LB, Holowaty EJ, Bergfeldt K, *et al.*, (1999). Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *New England Journal of Medicine* **340** 351- 357

Van Leewen FE, Chorus AM, Van Belt-Dusebout AW *et al.*, (1994). Leukemia risk following Hodgkin's disease: relation to cumulative dose of alkylating agents. Treatment with teniposide combinations, number of episodes of chemotherapy and bone marrow damage. *Journal of Clinical Oncology* **12** 1063 -1073