insights can be gained from investigation of therapy-related acute myeloid leukaemias (t-AMLs), which are becoming an increasing healthcare problem as more patients survive their primary cancers. Exposure to agents targeting DNA topoisomerase II (topoII) predisposes to the development of leukaemias with balanced translocations such as the t(15;17), fusing *PML* and *RARA* genes, in therapy-related acute promyelocytic leukaemia (t-APL) which is a recognised complication of cancer treatment particularly involving mitoxantrone and epirubicin.
Methods: t(15;17) genomic translocation breakpoints in t-APL were characterised by long-range PCR and sequence analysis. The mechanism underlying formation of observed breakpoints was investigated by functional *in vitro* topoII cleavage assays.
Results: We found that in t-APL cases arising in breast cancer patients exposed to mitoxantrone, chromosome 15 breakpoints clustered tightly in an 8bp "hotspot" region within *PML* intron 6, which was shown by functional assay to be a preferred site of mitoxantrone-induced DNA topoisomerase II cleavage (Mistry *et al*, N Engl J Med 2005;352:20−9). However, because cancer patients are typically exposed to multiple cytotoxic drugs often accompanied by radiotherapy, it is difficult to categorically ascribe the causative agent in any given patient with t-AML. Moreover, all previous studies have involved patient populations which could feasibly have been enriched for individuals at particular risk of leukaemia, having already developed one form of cancer. We therefore characterised t(15;17) genomic breakpoints in a cohort of t-APL cases arising in patients treated with mitoxantrone for a non-malignant condition i.e. progressive multiple sclerosis. Significant breakpoint clustering was also observed in this group, with 5 of 12 (42%) chromosome 15 breakpoints involving the "hotspot" within *PML* intron 6. Moreover, one of the chromosome 17 breakpoints occurring within the ~17kb *RARA* intron 2 was found to coincide with that of a previously identified t-APL case arising after mitoxantrone-containing treatment for breast cancer (Mistry *et al*, 2005). Analysis of *PML* and *RARA* genomic breakpoints in functional assays, including the shared *RARA* intron 2 breakpoint at 14444−48, confirmed each to be preferential sites of topoisomerase II-mediated DNA cleavage in the presence of mitoxantrone (Hasan *et al*, Blood 2008;112:3383−90). To investigate mechanisms underlying epirubicin associated t-APL, t(15;17) genomic breakpoints were characterised in 6 cases with prior breast cancer. Breakpoint clustering was again observed in *PML* and *RARA* loci, but *PML* breakpoints were found to fall outside the mitoxantrone-associated hotspot region. Recurrent breakpoints identified in the *PML* and *RARA* loci in epirubicin-related t-APL were shown to be preferential sites of topo II-induced DNA damage, enhanced by epirubicin.
Conclusion: Mitoxantrone and epirubicin exhibit site preference differences for DNA damage induced by topoisomerase II, which may underlie the propensity to develop specific molecularly defined subtypes of t-AML according to the particular chemotherapeutic agent used.

39 INVITED

Secondary leukaemia after breast cancer

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Secondary acute leukemia (sAL) is a well recognised complication of cytotoxic and radiation therapy for breast cancer with an incidence ranging from 0.1 to 1.5% in the reported series. In the archive of the Italian multicenter group for the treatment of hematologic malignancies (GIMEMA), more than 50% of patients with sAL had breast cancer, NHL, or HD as primary tumos. The high number of sAL observed in patients with a previous breast cancer, may be due to the fact that this malignancy is the most frequent neoplasm in women and by the high probability of cure with a consequent prolonged survival. Among treatments for the primary tumor, the association of alkylating agents and topoII inhibitors induced sAL with higher frequency, with cumulative risk at 3 years being 25±10%. According to a prospective Eastern Cooperative Oncology Group (ECOG) study, the use of standard dose cyclophosphamide did not increase the risk of sAL in patients with early stage breast cancer, whereas high doses of cyclophosphamide and doxorubicin were associated with significantly increased sAL development risk as did the combination of fluorouracil-doxorubicin-cyclophosphamide. Notoriously, radiotherapy can further enhance the risk of leukemia, while little is known about the risk of developing t-AL after treatment with novel agents such as monoclonal antibodies, anti-hormone drugs and small molecules. Although the causes predisposing to the development of s-AL are largely unknown, several genetic alterations and cooperating mutations have been identified that may play a role in the pathogenesis of this disease. In this context, individual predisposing factors, including polymorphisms in detoxification and DNA repair enzymes have been identified. As to genetic features of sAL, distinct clinical entities have been described according to the primary treatment, one comprising leukemias arising after alkylating agents which are associated with abnormalities of chromosome arms 5q and/or 7q, and a second group consisting of sAL occurring after topoII-targeting agents that are often associated with 11q23 (*MLL*) or 21q22 (*RUNX1*) or with translocations t(8;21), t(15;17) and with inv(16). The former group is characterized by long latency and poor response to therapy, while the second is associated with relatively short latency, absence of preceeding myelodysplastic features and favourable prognosis. This latter group also includes therapy related acute promyelocytic leukaemia (APL), a subset equally curable as the primary *de novo* disease with retinoic acid-based modern regimens. Survival of patients with s-AL after alkylating agents is extremely poor compared with that of patients with *de novo* AML. Because patients with s-AL have ben often excluded form front-line clinical trial, there is a paucity of prospective treatment data on treatment outcome. In addition, there are no randomized studies comparing standard AL chemotherapy with other treatment approaches. This notwithstanding, there is a general consensus on the view that the treatment most likely to cure t-AML is allogeneic stem cell transplantation. Criteria for therapeutic strategies in patients with s-AL should include the status of the primary cancer, performance status, and cytogenetic characterization of sAL. It is recommended finally that patients with s-AL be enrolled in prospective clinical trials in which therapeutic choices are differentiated according to their genetic features.

40 INVITED

Secondary leukaemia and myolodysplastic syndromes in patients successfully treated for Hodkgin lymphoma: a report from the German Hodgkin Study Group

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Treatment-related acute leukaemias (AK) and myelodysplastic syndromes (MDS) occur in patients successfully treated for various malignancies including breast cancer, testicular cancer, non-Hodkgin lymphoma and Hodgkin lymphoma. The prognosis of treatment-related AL and MDS is generally poor. At present, there is no clear treatment strategy for secondary AL/MDS in patients with HL. We thus evaluated the incidence and outcome of sAL/MDS from a total of 5411 patients treated in the trials HD1 – HD9 of the GHSG. After a median observation time of 55 months, the incidence of sAL/MDS was 1%. A total of 46 patients were identified with a median age of 47 years (22 – 79 years). 36 of the secondary malignancies were AL and 10 were MDS. The prognosis of these patients with sAL/MDS was very poor with disease-free survival of 2% and overall survival of 8% after 24 months of observation. An updated analysis with more patients and longer follow-up will be reported.

Special Session (Mon, 21 Sep, 14:00−15:00)
Case-based: linking symptom science to practice

41 INVITED

Symptom management: a case study

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Ms. S is a 60 year old woman undergoing treatment for breast cancer. She had a lumpectomy and lymph node dissection and has completed a course of radiation therapy. At the one month follow-up visit, she complains of burning and tingling in her surgical incision and axillary area, persistent fatigue, and sleep disturbance. This presentation will focus on the assessment of this patient's multiple symptoms and the development of an evidence-based intervention plan to manage her symptoms and improve her quality of life.

42 INVITED

Symptom clusters: a case study

E. Ream[1]. [1]*King's College London, The Florence Nightingale School of Nursing and Mid, London, United Kingdom*

A case study will be presented of a patient with complex symptoms, one of which was fatigue. Data relating to this patient will provide the focus for discussions over how symptom clusters should be managed. Participants will discuss various aspects of the process – for example assessment, self-management, multidisciplinary working, and engaging carers.