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

F. Lo-Coco[1], S.K. Hasan[1]. [1]*University of Rome Tor Vergata, Biopathology Department, Rome, Italy*

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

A. Engert[1]. [1]*Uniklinik Köln, Clinic I Internal Medicine Hematology/Oncology, Köln, Germany*

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

C. Miaskowski[1]. [1]*University of California San Francisco, Department of Physiological Nursing – School of Nursing, San Francisco, USA*

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.

Special Session (Mon, 21 Sep, 14:00−15:00)
Management of peritoneal disease

43 INVITED

Present and future of HIPEC (hyperthermic intraperitoneal chemotherapy) in colorectal carcinomatosis

D. Elias[1]. [1]*Institut Gustave Roussy, Villejuif, France*

In 2009, the treatment of colorectal peritoneal carcinomatosis (PC) with curative intent must be proposed in selected patients. More and more guidelines have included this therapy. The principle is to perform a complete cytoreductive surgery (CRS) to treat the visible tumour disease (>1 mm), and to use HIPEC to treat the non visible remaining tumour disease. HIPEC is contraindicated if the first step (complete cytoreductive surgery) is not reached. Postoperative mortality rate is acceptable, ranging from 4 to 8%. Two large multicenter registries including more than 500 patients treated with this combined approach reported median survival of more than 30 months and 5-year survival of more than 30% [1,2]. When considering the results of experimented centres, 5-year survival rate range between 40 and 50% [3−5]. This is similar to the results obtained with hepatectomy for liver metastases, leading us to consider that peritoneum is an organ like liver and that using the good therapy for each organ results in the same survival [6].
Indications of CRS plus HIPEC concerns the patients with a good general status, with no extraperitoneal localization and with a peritoneal score extent (Sugarbaker's index) lower than 20−24.Techniques of HIPEC are multiple and not yet standardized.
A randomized Dutch trial compared classical systemic chemotherapy to CRS + HIPEC with mitomycin C: 2-year survival rate was 16% in the control group versus 43% in the HIPEC group ($p = 0.01$) [7]. A non randomized study compared, for similar patients (PC was potentially resectable in both groups) recent sytemic chemotherapy to CRS +HIPEC with oxaliplatin: median survival was 24 months in the first group versus 63 months in the second [5]. So, the package CRS + HIPEC seems efficient, with a predominant impact of complete CRS. The next step is to appreciate the real impact of HIPEC by itself: a multicentric randomized trial is on going in France comparing, after complete CRS, HIPEC versus no HIPEC.
A new concept is to make effort to treat PC earlier. Treating PC at an early stage is less morbid and gives better survival. But the only way to early detect PC is to perform a second look. This was successfully proposed to patients presenting a high-risk to develop PC: asymptomatic PC was discovered and treated in 55% of the patients [8]. This study also showed that HIPEC should be performed even if no macroscopic PC was found. In these high-risk patients, a randomized trial comparing the classical attitude (adjuvant systemic chemotherapy alone) to the same plus second-look and HIPEC will begin soon.

References

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44 INVITED

Comprehensive management of gastrointestinal cancer: Focus on appendiceal mucinous neoplasms, primary gastric cancer and gastric cancer with peritoneal seeding

P. Sugarbaker[1]. [1]*Washington Cancer Institute, Surgical Oncology, Washington DC, USA*

Appendiceal mucinous neoplasms with peritoneal metastases are currently treated as a standard of care using cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. In order to make this assessment of data regarding management of this disease long term (20 year) follow-up was necessary.
Advanced gastric cancer at stage III or resected stage IV has a poor prognosis. A recent meta-analysis included randomized studies testing all forms of intraperitoneal chemotherapy. Ten were appropriate for data extraction. A significant improvement in survival was seen when chemotherapy was added to gastrectomy (HR = 0.60; 95% CI = 0.43−0.83; $p = 0.002$). The use of chemotherapy was associated with an increased risk of intraabdominal abscess and neutropenia.
In treating gastric cancer with peritoneal seeding, perioperative intraperitoneal chemotherapy when added to gastrectomy will prolong survival if the treatments can be safely completed. Patient selection for these modest improvements in survival is important because the treatments are of necessity very aggressive. There are a few long term survivors (10%).

Special Session (Mon, 21 Sep, 14:00−15:00)
Advances in fertility preservation for children and adolescents with cancer

45 INVITED

Improving success rates of sperm banking in adolescents

L. Schover[1]. [1]*UT M.D. Anderson Cancer Center, Department of Behavioural Science, Houston, USA*

Adolescent boys are excellent candidates for banking sperm before their cancer treatment. They often have malignancies, such as testicular cancer or Hodgkin lymphoma that have high rates of long-term survival. Once they have reached the stage of puberty in which spermatogenesis occurs, a number of recent surveys show that most have semen quality quite adequate for cryopreservation, particularly with modern infertility treatments such as in vitro fertilization with intracytoplasmic sperm injection.
However, the percentage of eligible teens who bank sperm is far from optimal. In many cancer centers in the United States and Europe. Some of the lack is due to failure to provide education and referrals on the part of the oncology treatment team. Recent efforts have focused on improving oncologists' knowledge about the benefits of sperm banking, producing appropriate patient education materials, and encouraging the involvement of oncology nurses and social workers in the process of counseling the family. It is also important to have a sperm bank either within the oncology treatment center or in a convenient location nearby. In the United States, some sperm banks offer express mail kits so that semen can be collected at home, mixed with a cryopreservative, and sent to a more distant laboratory. Some loss of semen quality is likely, but it is a better option than foregoing fertility preservation.
Patient and family factors also can be barriers to banking sperm. In the United States, out-of-pocket costs may not be affordable for poor or working class families, although some subsidies and payment plans are available. In Europe and Japan, sperm banking is typically covered under national health plans. More, often psychosocial barriers include fear that banking sperm will delay cancer treatment (despite the fact that even one stored sample is worthwhile), difficulty for young men in producing a sample by masturbation when they feel ill and have little privacy, the emotional pressure of feeling that they could be losing their chance to have a biological child if they cannot produce a sample, cultural and/or religious beliefs about masturbation and assisted reproduction, difficulty envisioning wanting to be a father later on in life, and emotional pressure from parents that can exacerbate the young man's anxiety. In one British study, teens were less likely to produce a semen sample when a parent accompanied them to the sperm bank.
A number of solutions can overcome these psychosocial barriers. A professional or slightly older peer counselor can discuss the semen collection process and suggest ways to feel more comfortable. Having a sound-proofed, homelike collection room with erotic magazines or DVD's is highly desirable. Teens can be encouraged to bring a personal music player to shut out noise and help with the mood. Any erotic materials furnished in the collection room should be soft core and conventional, although for teens who are gay, same-sex materials could be provided. Teens who are more sexually experienced could also bring their own DVDs and even a small DVD player. Depending on the age of consent in a country, the patient's committed partner could help in semen collection by providing manual stimulation. Having a vibrator available may also help.
For teens who are too ill or anxious to provide a semen sample, options include a medical grade vibrator, electroejaculation under anesthesia, or sperm extraction from the epididymis by a urologist or andrologist.

46 INVITED

Advances in ovarian cryopreservation

J. Donnez[1], M.M. Dolmans[1]. [1]*Université Catholique de Louvain, Department of Gynecology, Brussels, Belgium*

Advances in the diagnosis and treatment of childhood, adolescent and adult cancer have greatly increased the life expectancy of young women with cancer, but have resulted in a growing population of adolescent and adult long-term survivors of childhood malignancies, who may experience premature ovarian failure (POF) and infertility as a result of aggressive chemotherapy and radiotherapy treatments (indicated for both cancer and bone marrow transplantation (BMT)).