19 INVITED

Aggressive lymphomas: transatlantic approaches, challenges and opportunities

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Despite major strides in the treatment and investigation of aggressive non-Hodgkin's lymphomas (NHL) in the past several years, multiple challenges remain, some of which lead to opportunities for translatlantic cooperation. Incorporation of the anti-CD20 antibody, rituximab, has improved cure rates and survival in the most common subtype, diffuse large B-cell lymphoma (DLBCL) but further improvement is needed, particularly in patients with adverse clinical prognostic factors. Testing of a variety of new therapeutics and diagnostics is in process with a major question as to how to utilize the knowledge of the major molecular subtypes of DLBCL to assess these and to direct future drug development. Clinical questions or controversies in DLBCL that lend themselves to transatlantic activities include the choice of chemotherapy and use of radiotherapy in favorable, early stage DLBCL; choice and use of central nervous system prophylaxis; optimal therapies for individual extranodal presentations of DLBCL; and choice of drug therapy and use of radiotherapy in primary mediastinal large cell lymphoma, a distinct molecular subtype of DLBCL. Given that individually these DLBCL clinical subtypes and presentations represent rare entities, they invite international cooperation. In recent years, treatment of the high grade NHL in adults has been more successful with the adoption of strategies developed for the more common childhood and adolescent presentations of these disorders. As rare diseases, international cooperation is required for phase III investigations in the high grade NHL. Among the aggressive NHL, the most pressing need for clinical improvement is in the far less common T-cell lymphomas. There is considerable geographic variation in incidence for these disorders as well as a variable viral association. Further, resistance to chemotherapy characterizes some of these T-cell lymphomas, such as the natural killer/T-cell lymphomas whereas the angioimmunoblastic subtype is characterized by relative immune dysregulation. Plans have been initiated for an international group to establish a database for improved clinical and pathologic correlation and to provide the foundation for future international collaborations and clinical trials. As we recognize additional molecular subtypes on the basis of genome expression profiling, adding to the existing complexity of NHL classification, it becomes increasingly important to pair clinical data with informative tissue samples. Further, as we define more NHL subtypes and the absolute numbers of patients decline, the need for global cooperation in the study of new, targeted therapeutic approaches will further increase.

20 INVITED

Hodgkin's disease and indolent lymphomas: transatlantic approaches and opportunities

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Hodgkin's lymphomas (HL) belong to the most curable adulthood cancers with a cure rate of nearly 85–90% in all stages of the disease. While in Europe most cooperative study groups use a risk stratified treatment strategy according to anatomical stage, clinical risk factors and tumor burden with the differentiation in **early, intermediate and advanced stages**, most transatlantic Northamerican study groups discriminate according to anatomical stage, B-symptoms and bulky tumor between two treatment strata: **early (localized) and advanced Hodgkin lymphoma.** This means that about 30% of the intermediate (GHSG) or early unfavorable (EORTC) stage patients with a 5 year tumorfree survival of 90% and a 96% overall survival rate with a standard combined chemo–radiotherapy of 4 cycles of ABVD + 20–30 Gy IF-RT will be treated in North America with 6–8 cycles of ABVD or similar rgimens +/– RT. In advanced stages there is a controversial discussion transatlantically whether ABVD is considered the gold standard treatment with a FFTF of 65–70% and a OS of 75–80% at 5 years. The EORTC, ECOG, Australian and Scandinavian groups at the moment test ABVD versus escalated BEACOPP, a time and dose intensified regimen based on COPP/ABVD.

Follicular lymphomas are the second most common NHLs. The course of the disease is indolent, cures, however, are rare. There is a global endeavour within European and North American multicenter studies to prove whether more aggressive approaches than the watch and wait or the single drug therapy (chlorambucil) or the mild CVP-(cyclophosphamide, vincristine and prednisone) therapy yield higher CR rates, better tumor free survival and hence possibly on the long run higher cure rates. New approaches tested intensively in prospective multi center studies use Fludarabine based regimens, CD20- antibody (Rituximab) in combination with chemotherapy (CVP,CHOP, FMP), radioimmunotherapy (131-I-anti CD-20: Bexxar; 90-Y-anti CD20: Zevalin) for therapy naïve or relapsing patients. These pivotal studies soon will tell us the impact on survival of patients with FL. Current studies on both sides of the Atlantic are on the way and shall give us the badly needed information whether high dose chemotherapy treatment followed by autologous or allogeneic stem cell grafting with or without myeloablative conditioning will yield higher long term response, if not cure rates, or whether these approaches are ameliorated by adverse lethal side effects following aggressive strategies, leading to secondary AML/MDS and toxic organ damages.

Scientific Symposium
Hereditary cancers: the implementation of knowledge in clinical practice (breast, colorectal, ovarium)

21 Abstract not received

22 INVITED

Counselling/decision processes: the practice and purpose of genetic counselling

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The purpose of genetic counselling is to inform patients or relatives at risk of a disorder that may be hereditary of the consequences of that disorder, the probability of transmitting it and of the ways in which the consequences can be prevented, avoided or ameliorated. For genetic predisposition to cancer there are several distinct stages of the counseling process. Evaluation of the evidence for or against a genetic predisposition and the likely mechanism of inheritance (if any) inform which strategies aimed at early detection or prevention may be appropriate. Molecular genetic testing may refine the risk assessment and allow more specific risks to be given to individuals. Information can assist in decision making but also into this equation comes the personal health beliefs and coping strategies of the individual being counseled and their experiences of other family members illness and treatment. The genetic counseling process must allow adequate time for reflection and consideration of the potential impact of each stage of the process to ensure that the outcome of this process is as constructive as possible.

23 INVITED

How to reduce the risk of hereditary ovarian cancer

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Family history is an important risk factor for ovarian cancer. Compared to the lifetime risk of 1.7% for the general population, the probability of developing ovarian cancer may be 27% (BRCA2) or even 60% (BRCA1) in hereditary syndromes. The most frequent hereditary ovarian cancer occurs in the familial breast and ovarian cancer syndrome (BRCA1 or BRCA2 gene), less frequently in the HNPCC syndrome (mismatch repair genes MLH1 and MSH2) and rarely in the Li-Fraumeni syndrome (p53 germline mutation). More than 10% of ovarian cancers develop on a hereditary basis. As for risk reduction, retrospective analyses have demonstrated a risk reduction by 60% after 6 years of oral contraceptive use in BRCA1/2 carriers. This effect also correlated with the time of use (p for trend, $p < 0.001$). Tubal ligation reduces the risk not only of sporadic but also of familial ovarian cancer by 61% (95%CI: 0.22–0.70; $p = 0.002$). Hysterectomy reduces the ovarian cancer risk by 50% and can be offered to women of HNPCC families (endometrial cancer is second most frequent manifestation following colon cancer) or to women with particular BRCA1 mutations conferring high risk of endometrial cancer or to women who wish to use tamoxifen for breast cancer prevention after prophylactic bilateral salpingo-oophorectomy (PBSO). Laparoscopic PBSO eliminates the risk of ovarian but not of primary peritoneal cancer which is increased in BRCA carriers. Ablative measures will be most risk reducing when undertaken earlier in life, at the age of 40. Quality of life may be particularly increased in women who are convinced of the preventive nature of the surgery (plus 4.4 quality adjusted life years QALY, Markov model).

24 INVITED

Specific issues in breast cancer

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Nowadays, the major tasks of the increasing number of family cancer clinics are to provide general information about (breast) cancer, to perform risk

assessment, to offer (presymptomatic) DNA-testing, to advise on lifestyle, to take steps for early detection and prevention of cancer, for psychological support and to carry out research programmes by a multidisciplinary approach. In approximately 25–30% of the families with a hereditary pattern of breast cancer a germline mutation (in BRCA1, BRCA2, P53, CHEK2 or other genes) can be demonstrated. This percentage varies between 5% and 80% depending on the composition of the pedigree and age of onsett of different cancer types. Mutations in these genes are associated with high life-time risks of breast and ovarian cancer. The introduction of MRI increased the sensitivity for detection of early breast cancer with more favourable tumour stages in comparison with mammography. The value of screening on early ovarian cancer is unproven and probably low. Thusfar, prophylactic bilateral total mastectomy is the most effective and safest way of prevention but prophylactic adnectomy and chemoprevention are reasonable alternatives. Each method of breast cancer prevention has its own specific side effects and psychological problems. Especially young women with children make use of DNA-testing and surgical prevention. Recent studies show that hereditary (metastatic) breast cancer need specific standard and experimental systemic therapy. By a shared decision-making process, the patient and her doctor have to make the right choices of management policy based on her individual circumstances.

25 INVITED

Specific issues in colon cancer

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Colorectal cancers are a major killer, their genetics is well understood and both curative and preventive surgery are well established. The accessibility of precancerous polyps to colonoscopy and the difficulty of offering this invasive procedure to a wide population make targeting on the basis of genetic testing a credible use of health resources. European diet and lifestyle predispose to this cancer and offer realistic strategies for chemoprevention. The European led CAPP consortium is now testing aspirin and resistant starch is possible agents for more general use. The first study, CAPP1, in over 200 FAP gene carriers showed some beneficial effects. Three recent reports have dispalyed beneficial effects of aspirin in patients with previous polyps or previous cancer. Our current study CAPP2 (see *http://www.capp2.com/*) has now recruited over 1000 proven carriers of HNPCC (Lynch syndrome)either on the basis of being an affected member of an Amsterdam positive family or having a known pathological mutation in a mismatch repair gene or both. All participants take 600 mg of aspirin and/or 30 grams of the resistant maize starch Novelose from one surveillance colonoscopy until their further examination at 2 years. Over half agreed to continue the treatment up to 4 years. The results will be available in summer 2007.
Other possible agents for the next genetically targeted trial include curcumin, selenium, statins, and calcium. The use of selective coxibs has suffered a major setback due to unexpected cardiovascular side effects in recent sporadic polyp prevention trials illustrating the major challenge in prevention to find agents which are effective, cheap and safe.

Scientific Symposium
Prevention and early diagnosis of cervical cancer – a paradigm?!

26 INVITED

Can HPV testing challenge the PAP smear?

J. Cuzick. *Cancer Research UK Department of Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, London, United Kingdom*

Cervical screening has been the most successful cancer prevention programme ever implemented. However the approach does have limitations in terms of the infrastructure and expertise required, and is now more that 50 years old.
The human papilloma virus is now established as the primary cause in over 95% of all cervix cancers worldwide. It is readily detectable in material collected in a smear, and is an obvious candidate for screening. There are three potential roles for the test

i. Improving management in women with borderline or mildly dyskaryotic smears.
ii. Post-treatment surveillance to detect incomplete excision on CIN
iii. As a part of primary screening to improve sensitivity

Use in the first two situations is scientifically well established, but the use of HPV in primary screening is more controversial. Several studies have shown that HPV has a much higher sensitivity for histologic CIN2+ than cytology and is much more reproducible. However its specificity is lower. These observations support the use of HPV testing as the sole primary screening modality, with cytology reserved for the triage of HPV positive women. The data supporting this claim and issues related to implementation such as age at commencement of screening and interval between tests will be discussed. A potential algorithm for this new approach will be presented.

27 INVITED

Efficiency and effectiveness of cervical screening with cytology

M. Hakama. *University of Tampere School of Public Health, Finland*

The data available on effect of screening with cytology come from observational studies of screening in defined populations. cohort and case-control studies, which may not be free of bias, and studies of incidence and mortality trends which could be affected by changes in risk factors for the disease.
Studies using cohort, case-control of geographical correlation (before/after analysis) designs indicate substantial effects in reducing the cervical cancer incidence and mortality rates, the impact exceeding 80% among women screened in various organized settings. Studies in the Nordic countries, the United Kingdom and Canada, have been most informative. There is evidence that the screening impact is particularly large in the organized screening programmes. Opportunistic screening has been found to reduce cervical cancer incidence to a smaller extent than organized programmes, and requires far more resources.
The incidence of invasive cancer of the cervix is low in women aged less than 25, while in women aged 25–34 there is a low absolute risk of invasive cancer of the cervix after a negative screening test during the following three years. In women over the age of 35, and especially over the age of 50, the risk of invasive cancer of the cervix after a negative test is low for the next five years. The evidence does not support screening after the age of 65 in cytologically negative women.
The cytology test has been shown to be effective when well applied. Where cytology screening has failed to work, blame can be laid on the design or delivery of the screening service. Health services research can and should be used to ensure that screening of proven efficacy is implemented in an optimal manner for a given population.
Time trends in the incidence and mortality rates of cervical cancer are of considerable interest, as they provide a means of evaluating the effectiveness of screening programmes. Comparisons of trends in the Nordic countries have been particularly informative. Decreases in incidence and mortality since the late 1960s were greatest in Finland, Sweden and Iceland, which had the most extensive screening programmes, and least in Norway, which had organized screening only in one county. Observation of these trends has sometimes (e.g., in the United Kingdom) resulted in changes in screening practices. Cervical cancer mortality rates have been rapidly rising in a number of eastern European countries where there is little screening.
In summary, screening for cervical cancer every 3–5 years between the ages of 35 and 64 years by conventional cytology in a high-quality programme reduces the incidence of invasive cervical cancer by 80% or more among the women screened. Screening in well organized programmes is more cost-effective, with less harm due to overscreening and overtreatment, than opportunistic screening.

28 INVITED

Cervical cancer: aetiology and prevention strategies

X. Bosch. *IDIBELL-Institut Català d'Oncologia, Servicio de Epidemiologia y Registro Cancer, Barcelona, Spain*

HPV vaccines for the prevention of persistent HPV infections seem to be a major step forward in cervical cancer prevention and the only realistic option for developing countries. Since HPV type-specific cross protection is limited, one of the central issues in exploring products destined to widespread use is the number of viral types that are to be included. Current vaccines under evaluation include HPV 16 and 18 (GSK) and HPV 16,18, 6 and 11 (MSD). The expected protection against cervical cancer among vaccinated women would account for close to 70%. In addition, HPV 6/11 containing vaccines would offer protection against the vast majority of Genital Warts, a common sexually transmitted infection. A vaccine that would include the seven most common HPV types in cervical cancer (HPV 16, 18, 45, 31, 33, 52 and 58) would effectively prevent 87% of the cases to be among vaccinated women.