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.

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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