session 1 – 50th anniversary of Burkitt lymphoma

006 50TH ANNIVERSARY OF THE DISCOVERY OF BURKITT LYMPHOMA: HISTORY AND BIOLOGY

I.T. Magrath[1]
[1]International Network for Cancer Treatment and Research, Brussels, Belgium

Burkitt lymphoma (BL) was discovered 50 years ago when there was limited understanding of the immune system, no comprehension of the molecular mechanisms of disease and few tools available for studying the biology of cancer. BL, literally ''put on the map'' by Burkitt and colleagues in the late 1950s and 1960s, provided a valuable paradigm for the understanding of environmental and genetic factors in lymphomagenesis. Through primitive but effective epidemiological studies, which included writing to or visiting a large number of hospitals in Africa, Burkitt and colleagues showed the distribution of the tumor to be limited by temperature and rainfall, similar to several insect-vectored infectious diseases. This suggested that the disease may be caused by a virus, as had been shown to be the case in some animal tumors, and led to the discovery of the first human tumor virus, Epstein-Barr virus (EBV), in cell lines derived from tumor samples sent to London from Kampala. The Henle's demonstrated that EBV infection is highly prevalent, but patients with Burkitt lymphoma have higher antibody titres to ''lytic'' EBV antigens than control populations, indicating that EBV may be of pathogenetic relevance but is not a sufficient cause. Moreover, since EBV is not transmitted by insects, it cannot explain the climatically-determined distribution of BL. Dalldorf's alternative proposal, that malaria predisposes to BL, is now well supported by both epidemiological and laboratory studies. Both EBV infection and malaria occur in infants in Africa. BL incidence correlates with the intensity of malarial infection; malaria increases the proportion of circulating B lymphocytes infected by EBV. The discovery of Ig-mcy translocations in BL led to the recognition of the central role of deregulated c-myc in promoting cell proliferation. Experimental data suggest that EBV may allow cells containing c-myc translocations to survive – a role doubtless served by other genetic abnormalities in low incidence EBV-negative tumors. Recently published gene expression profiling has provided a new, objective definition of BL and clarified the indistinct morphological boundary between BL and diffuse large B cell lymphoma (DLBCL). Morphologically intermediate lymphomas, referred to as atypical BL, and some DLBCL, have the molecular profile of BL (mBL), whereas genetically intermediate lymphomas are predominantly morphologically DLBCL. Interestingly, some mBLs have non-Ig translocations and some no myc translocation at all, indicating that multiple pathogenetic pathways can lead to BL.

007 CONSERVED ONCOGENIC MODULE ACTIVATION PATTERNS (COMAPS) IDENTIFY BIOLOGICALLY HOMOGENEOUS GROUPS OF DIFFUSE LARGE B-CELL LYMPHOMAS AND CLEARLY DEFINE BURKITT LYMPHOMA

S. Bentink[1], S. Wessendorf[2], C. Schwaenen[2], M. Rosolowski[3], W. Klapper[4], A. Rosenwald[5], G. Ott[6], A. H. Banham[7], M. Hummel[8], M. Loeffler[3], L. Truemper[9], H. Stein[8], R. Siebert[10], R. Spang[1]
[1]Institute of Functional Genomics, University of Regensburg, Regensburg, Germany, [2]Internal Medicine III, University Hospital Ulm, Ulm, Germany, [3]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany, [4]Institute of Hematopathology, University of Kiel, Kiel, Germany, [5]Institute of Pathology, University of Würzburg, Würzburg, Germany, [6]Department of Clinical Pathology, Robert-Bosch-Krankenhaus, Stuttgart, Germany, [7]Nuffield Department of Clinical Laboratory Sciences, University of Oxford, Oxford, UK, [8]Institute of Pathology, Charité, Campus Benjamin Franklin, Berlin, Germany, [9]Department of Hematology and Oncology, University of Göttingen, Göttingen, Germany, [10]Institute of Human Genetics, University of Kiel, Kiel, Germany

Introduction: Modern targeted cancer drugs intervene in cell signaling pathways by compensating for their deregulation. Hence, the characterization of signaling activity in tumors will become crucial for treatment decisions.

Methods: 220 mature aggressive B-cell lymphomas were screened for the activity of oncogenic transcriptional modules, using data previously derived from human primary epithelial cell lines (HMECs) transfected with either *MYC*, *RAS*, *SRC*, *E2F3*, or *ß-catenin*. Our novel bioinformatics approach successfully overcame the substantial differences between the transcriptional programs of lymphoid tumors and epithelial cells to clearly define oncogenic modules.

Results: We identified transcriptional modules predictive of oncogenic activation status that are strongly conserved between HMECs, diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL). BL was characterized by a unique conserved oncogenic module activation pattern (COMAP) derived from the activity constellations of *MYC*, *RAS*, *SRC*, and *E2F3*. DLBCLs and their subgroups were heterogeneous with respect to pathway activation subdividing into four recurrent pathway activation constellations, which significantly correlated with the presence of recurrent chromosomal aberrations.

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008 RECENT RESULTS IN THE TREATMENT OF BURKITT LYMPHOMAS

D. Hoelzer[1]
[1]Dept. Onkologie/Hämatologie, Klinikum der J.W. Goethe Universität, Frankfurt / Germany
On behalf of the German Multicenter Study Group for Adult ALL

With short intensive chemotherapy regimen derived from pediatric protocols and mainly based on HDMTX, fractionated HD alkylating agents and HDAC, the outcome of Burkitt s NHL and mature B-ALL (B-ALL) in adults could be substantially improved to CR rates of 80% and overall survival of about 50-60%. Further intensification namely increase of MTX dose failed to improve these results. Thus in the GMALL trial B-NHL 90 with 6 intensive chemo cycles, the overall survival of 272 pts including mainly Burkitt NHL, mature B-ALL and DLBCL was 56%. Therefore the German Multicenter Study Group for Adult ALL (GMALL) invented in 2002 a new protocol for mature B-ALL/Burkitt and other high-grade NHL, namely primary mediastinal (med) DLBCL. It consisted of 6x Rituximab® 375 mg/m^2 before each chemo cycle and two R maintenance cycles. In addition 2 cycles based on HDAC 2 g/m^2 were included. HDMTX was 1,5 g/m^2 in the protocol for younger pts (<55 yrs). Older pts (>55 yrs) received a dose reduced regimen without HDAC and with MTX at 500 mg/m^2. 332 pts with Burkitt (32=Burkitt-like), B-ALL or DLBCL aged between 16 and 78 enrolled between 09/02 and 10/07 were evaluable for response after the first two cycles. The median age was 36 yrs for Burkitt, 46 for B-ALL and 35 for DLBCL; 18%, 41% and 12% were older than 55 yrs respectively. The subgroups were characterised as follows: 146 Burkitt (stage III-IV 52%, extranodal inv. 78%, aaIPI >1 47%), 84 mature B-ALL, 102 DLBCL (stage III-IV 55%, extranodal inv. 71%, aaIPI >1 61%). The CR rate was 90% in Burkitt, 83% in B-ALL and 69% in DLBCL; death under therapy occurred in 3%, 11% and 0% respectively. The overall survival at 3 yrs was 91% for Burkitt, 79% for B-ALL and 90% for med DLBCL in pts at the age of 15-55 yrs and 84%, 39% and 67% (N=5) respectively in pts >55 yrs. There was no difference in OS between pts with Burkitt (93%) vs Burkitt-like NHL (91%). Major grade III/IV toxicity was hematological (28-37%) and mucositis (36%, 37%, 28% in cycles A1, B1, C1 respectively. In this largest prospective study of adult Burkitt's lymphoma/leukemia the combination of Rituximab and 6 short intensive chemo cycles was feasible and lead to an substantial improvement in the overall survival in younger as well as in older pts 84% with Burkitt's NHL. Aims of the next generation of B-NHL study is 1) Reduction of mucositis, 2) Reduction of the number of cycles in good responders, 3) Redefinition of response evaluation by analysis of Minimal Residual Disease and PET, and 4) further extended application of the protocol in HIV+ Burkitt NHL pts.

009 A PROSPECTIVE STUDY OF DOSE-ADJUSTED (DA) EPOCH WITH RITUXIMAB IN ADULTS WITH NEWLY DIAGNOSED BURKITT LYMPHOMA: A REGIMEN WITH HIGH EFFICACY AND LOW TOXICITY

K. Dunleavy[1], R.F. Little[1], S. Pittaluga[1], N. Grant[1], M. Shovlin[1], S. Steinberg[1], R. Yarchoan[1], J. Janik[1], E.S. Jaffe[1], W.H. Wilson[1]
[1]Center for Cancer Research, National Cancer Institute, Bethesda, United States

Background: Burkitt lymphoma (BL) is a rare and very aggressive lymphoma, characterized by a high tumor proliferative rate. ''Standard'' therapy of BL is highly effective but involves intensive, multi-agent chemotherapy that is associated with high treatment related toxicity and mortality, particularly in older patients. We hypothesized that the DA-EPOCH-R regimen may be effective in BL, given its established efficacy in DLBCL and its ability to overcome highly proliferative tumors.

Methods: We set out to investigate if DA-EPOCH-R could maintain the high cure rates of standard therapy in BL while minimizing treatment related toxicity. Eligible patients had untreated BL and could be HIV negative or positive - HIV negative patients (n=15) received 6 cycles of DA-EPOCH (with Rituximab) as previously described (Blood 99: 2685, 2002) and HIV positive patients (n=8) received 3-6 cycles of DA-EPOCH-R for 1 cycle beyond CR for a minimum of 3 cycles (Blood 106: #930, 2005). All patients received intrathecal methotrexate prophylaxis and outpatient therapy was instituted where possible.

Results: Characteristics of 23 enrolled patients are: median age (range) 31 (18-66); male sex 18 (78%); median (range) ECOG PS 1 (1-3); stage III/IV 12 (52%); LDH > N 12 (52%); extranodal sites 17 (74%) and ileocecal disease 15 (65%). No patients had CNS involvement at diagnosis. Responses are CR/CRu in 100% with one patient

receiving consolidative radiation to a site of residual disease. OS and PFS are both 100% and EFS 95% at a median potential follow-up of 27 months. Significant toxicities included tumor lysis syndrome (TLS) in one patient and fever/neutropenia in 16% of cycles. There were no treatment related deaths.

Conclusions: DA-EPOCH-R is a very effective and well tolerated regimen in the treatment of newly diagnosed BL and is associated with low toxicity and low rates of TLS compared to "standard" high dose regimens used in BL. This regimen may significantly advance the therapeutic index in the treatment of BL. Accrual continues.