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Third annual forum on T-cell lymphoma

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Third Annual T-cell Lymphoma Forum
San Francisco, CA, USA, 27–29 January 2011

The Third Annual T-cell Lymphoma Forum, held on 27–29 January 2011 in San Francisco (CA, USA), continued in the spirit of the two earlier conferences and provided a collegial venue for clinicians and scientists to discuss advances in the science and treatment of T-cell lymphomas. More than 40 experts from around the world presented updates on classification, epidemiology and prognosis; rare and T-cell lymphomas of unspecified origin, CD30$^+$ T-cell lymphomas; new treatment strategies; new agents and rational combinations; and transplantation. Of particular interest this year was a discussion on the link between breast implants and anaplastic large-cell lymphoma, which coincided with the US FDA announcement of this rare but noteworthy relationship. Submitted abstracts and poster presentations rounded off each of the sessions.

Conference history

The T-cell Lymphoma Forum was first held in Washington (DC, USA) in 2008 to share the latest research, exchange ideas and increase exposure for these rare types of lymphomas. The second forum, held in Hawaii (USA) in 2010, continued the momentum begun by the first conference and focused on epidemiologic and clinicopathologic characteristics of and treatment strategies for T-cell and natural killer (NK)-cell lymphomas. The third forum, held on 27–29 January 2011 in San Francisco (CA, USA) under the chairmanship of Francine Foss of the Yale Cancer Center in New Haven (CT, USA) and Kensei Tobinai, once again provided a platform for discussion about the classification, epidemiology, prognosis and pathogenesis of several T-cell lymphoma subtypes, and novel agents and treatment approaches. The conferences are designed for hematologists, oncologists, and other clinicians and scientists interested in T-cell lymphoma research and treatment. All three conferences have encouraged participation in T-cell registries and collaborations. The fourth T-cell lymphoma forum is scheduled for January 2012.

Classification, epidemiology & prognosis

James O Armitage (University of Nebraska, NE, USA) delivered the keynote address on classifying T-cell lymphomas. The difficulty in characterizing peripheral T-cell lymphomas (PTCLs) is that clonality is difficult to establish, variable immunological patterns exist, cytogenetics are only occasionally characteristic, and there are few characteristic oncogenes. In addition, as new treatments emerge, the optimal system established today for classification will most likely become obsolete. Lymphoma classification remains a moving target.

Dan Jones (Quest Diagnostics Nichols Institute, VA, USA) stressed the importance of T-cell function in the classification of T-cell lymphomas. Both clinicopathologic elements and molecular genetic entities must be considered in classifying post-thymic T-cell malignancies. For example, tumor types that overexpress the T-cell oncogenes *ALK*, *TCL1* and *SYK* bypass the upstream regulatory function of the T-cell pathway, and will most likely require different kinds of immunomodulation and different therapy targets.

Gene-expression profiling studies with large datasets and linkage to clinical outcome data are beginning to emerge that will help determine gene signatures that impact survival. Randy D Gascoyne (British Columbia Cancer Agency, BC, Canada) discussed recent work from the International Peripheral T-cell Lymphoma Project and gene signatures that impact survival in the angioimmunoblastic T-cell lymphoma (AITL) subtype [1]. He also discussed novel translocations in PTCL, such as those that target the IRF4/MUM1 locus on chromosome 6p25 [2], the identification of which may be important to T-cell biology and survival predictions.

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Rare & T-cell lymphomas of unspecified origin

T-cell lymphomas represent approximately 40% of all non-Hodgkin's lymphoma in children and adolescents, and more than 90% occur in the three subtypes of T-lymphoblastic lymphoma, systemic T-anaplastic large-cell lymphoma (ALCL) and PTCLs not otherwise specified [3]. Mitchell S Cairo (Columbia University, NY, USA) discussed the characteristics of each of these subtypes, recent investigations, and the novel therapies for each, such as nelarabine, vinblastine and brentuximab vedotin.

Christian Gisselbrecht (Institut d'Hématologie, Hôpital Saint Louis, Paris, France) presented data on rare T-cell lymphomas collected through a comprehensive translational program launched in 2008 by pathologists with data from the Groupe d'Etude des Lymphomes de l'Adulte (GELA), Groupe Ouest-Est des Leucémies et Autres Maladies du Sang (GOELAMS) and Société Française des Cancers de L'Enfant (SFCE) centers. The program collected over 605 frozen PTCL samples with corresponding clinical data. Preliminary results describe some major pathways important for rational use and design of new drugs. Prospective collection of *de novo*, clinical and histological material is ongoing.

Gene-expression profiling revealed a distinct molecular signature for one of the rare types of T-cell lymphoma, namely, hepatosplenic T-cell lymphomas, as described by Marion Travert (Hôpital Henri Mondor, Créteil, France) in a poster presentation. A comparison of hepatosplenic T-cell lymphoma cells with normal γδ T cells found overexpression of genes encoding NK cell-associated molecules (*NCAM1*), oncogenes (*MAFB*, *FOS* and *JUN*), multidrug-resistance molecules (*ABCB1*), tyrosine kinases (*SYK*) and others. Among the dowregulated genes were those associated with activated cytotoxic molecules, tumor-suppressor genes (*AIM1*) and CD5.

CD30$^+$ T-cell lymphomas

Lauren C Pinter-Brown (Geffen School of Medicine at UCLA, CA, USA) discussed CD30$^+$ diseases of the skin, including the newly recognized entity of ALCL surrounding breast implants. Primary breast lymphomas are extremely rare, representing 0.04–0.05% of all breast malignancies. Of these, less than 5% are T-cell lymphomas. Of the 36 reported cases of NHLs associated with breast implants, 81% were ALCLs, and 100% of the cases with anaplastic lymphoma receptor tyrosine kinase (ALK) data were ALK negative. The implants had been in place for an average of 6.9 years. One reason for the association may be the textured surface of the implants, both saline and gel. Study of implants removed for various reasons shows that most cases are localized to the capsule and/or a seroma within the fibrous capsular space.

Max Robinowitz (Division of Immunology and Hematology Devices, US FDA) expanded on the FDA announcement that coincided with the Forum. He said that the FDA is working with the American Society of Plastic Surgeons and many of the clinical experts at the forum to establish a patient registry of ALCL associated with breast implants. ALCL should be suspected if a patient develops a late seroma, swelling, asymmetry or contracture adjacent to her breast implant years after the breast implant incision is fully healed.

Barbara Pro (Fox Chase Cancer Center, PA, USA) reported the interim results of a Phase II study of brentuximab vedotin (SGN-35) in 58 relapsed or refractory systemic ALCL patients. The overall response rate (ORR) by an independent review panel was 86%, with 53% complete remissions. Median duration of response and survival has not yet been reached. Brentuximab vedotin resulted in complete remissions (CRs) in 50% of both ALK-negative and -positive patients. Adverse events were manageable, including peripheral neuropathy, and the investigators concluded that brentuximab vedotin is a promising new agent for CD30$^+$ malignancies.

New treatment strategies

Adult T-cell leukemia-lymphoma (ATL) is associated with human T-cell lymphotropic virus type 1 and has the worst prognosis among various PTCLs according to the International T-Cell Lymphoma Project [4]. Southwestern Japan has the highest prevalence of human T-cell lymphotropic virus type 1 infection and the highest incidence of ATL in the world. Among the new agents targeting ATL is KW-0761, a humanized anti-CCR4 antibody, which produced an overall response rate of 31% in a Phase I study [5]. A Phase II study is underway. KW-0761 is also being studied in combination with VCAP–AMP–VECP. The latter chemotherapy regimen followed by allogeneic stem cell transplant is also being evaluated for untreated aggressive ATL. In addition, a Phase III study is being planned to compare zidovudine plus IFN-α with watchful waiting for indolent ATL.

In a poster presentation, Madeleine Duvic (University of Texas MD Anderson Cancer Center, TX, USA) presented the preliminary results of a Phase II study of KW-0761 in cutaneous T-cell lymphoma and PTCL, excluding ATL. Of 32 evaluable patients, the ORR was 38%, with three patients achieving CR.

New agents & rational combinations

A plethora of new drugs and combinations have been or are being developed, representing a crucial step forward in the treatment of PTCL. Among them are the histone deacetylase inhibitors (HDIs), particularly panobinostat, belinostat, romidepsin and vorinostat. Susan E Bates (National Cancer Institute, MD, USA) pointed out that while the HDIs are similar, they are not the same, having different affinities for the histone deacetylases. She discussed the remarkable sensitivity of HDIs in T-cell lymphoma, and described the potential relationship with the increased expression of pro-apoptotic proteins with inhibitors of cell cycle progression due to direct effects on chromatin.

Purine nucleoside analogs are another class of novel agent for T-cell lymphomas, and Duvic presented information on these promising agents, in particular, gemcitabine, pentostatin, fludarabine, nelarabine and the newly synthesized forodesine. A dose-escalating Phase I/II trial of oral forodesine achieved an ORR of 39%, with acceptable safety profiles in cutaneous T-cell lymphoma patients. A Phase II trial in 120 patients has been completed.

Steven M Horwitz (Memorial Sloan–Kettering Cancer Center, NY, USA), in addition to a discussion of folate analogs, presented a poster on the results of a Phase II study of romidepsin in progressive

or relapsed PTCL following prior systemic therapy. The ORR was 26% as confirmed by an independent review committee, with 13% of the 130 patients achieving CR. The median duration of response was 12 months for the entire responding population.

Transplantation

Stem cell transplantation is potentially a curative treatment option for patients with relapsed/refractory PTCL and for those with poor prognosis subtypes. Foss reviewed the role of reduced-intensity (RI) regimens in allogeneic transplant, which has not been fully explored in PTCL. In a registry review of data reported to the Center for International Blood and Marrow Transplant Research on RI transplants performed between 1996 and 2005, there were no significant differences in the transplant-related outcomes when comparing reduced conditioning with myeloablative [6]. A retrospective study by the Société Française de Greffe de Moëlle et de Thérapie Cellulaire (France) found no impact of conditioning regimen on overall or event-free survival [7]. In addition, in a series reported by the European Group for Blood and Marrow Transplantation in patients with relapsed and refractory AITL, there was again no difference between ablative and RI conditioning in terms of overall survival and progression-free survival [8]. Other trials are being planned using RI regimens.

Andrei R Shustov (Fred Hutchinson Cancer Research Center, WA, USA) discussed who should receive autologous transplantation and when in T/NK-cell lymphomas. After reviewing the evidence from a number of retrospective and prospective clinical trials, Shustov concluded that high-dose therapy (HDT) with autologous hematopoietic cell transplant (aHCT) is feasible in primary therapy of T/NK-cell lymphoma, but current evidence does not support the routine use of HDT–aHCT in all patients, although relapses eventually occur in the majority of them. Shustov said that patients with AITL might benefit from upfront HDT–aHCT, but patients with high-risk PTCL might not benefit and should be treated in clinical trials. HDT–aHCT might be appropriate for patients who achieve a partial remission after initial therapy. Prospective randomized trials are needed to define the role of HDT–aHCT in T/NK-cell lymphoma.

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