Session 5: lymphoma and the immune system

061 INTRODUCTORY LECTURE

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Most lymphomas derive from B lymphocytes and continue to occupy lymphoid niches. The drive on B cells by persistent pathogens sets the scene for tumorigenesis and, at early stages, may be reversed using anti-infectives. The surface immunoglobulin (sIg), a key receptor of B cells, is retained and functional, indicating its importance for tumor cell growth and survival. Chronic activation, likely mediated by environmental factors in early disease, may continue later via activating mutations.

The sIg variable (V) region gene sequences provide insight into the cell of origin. The importance of this is illustrated by the two subsets of chronic lymphocytic leukemia with unmutated or mutated IgV genes, which have distinct clinical courses. There are other intriguing features of sIg, especially in follicular lymphoma where the vast majority of cases acquire sites for glycan addition in the IgV regions. These glycans are of unusual high mannose form, suggesting interaction with local lectin-bearing cells, possibly macrophages, known to be linked to poor prognosis.

Immune control of lymphoma may explain spontaneous remission or dormancy in low grade disease, and is evident in GvL effects following allotransplantation. For immunotherapy, the idiotypic (Id) determinants provide a tempting target. The success of anti-CD20 indicates that lymphoma cells are susceptible to antibody attack, and the biological ideal would be to use passive anti-Id antibodies. These would be tumor-specific and would attack the critical receptor expressed by lymphoma cells. Despite clinical evidence of success, the need for patient-specific antibodies made this approach impractical, but an alternative strategy to generate antibodies or small molecules to block the interactions mediated by the unusual sIg glycans, common to all cases, may hold promise.

Turning the immune system against itself by vaccination is more challenging, but has the added goal of inducing lasting protection against tumor emergence. Trials of idiotype vaccines have been largely disappointing, and the clinical setting is now dominated by anti-CD20, rendering the immune system even less capable of responding to vaccination. Induction of cytolytic T cells may be feasible but V regions carry a myriad of mutated sequences and the problem iswhich, if any, would bind to the MHC Class I molecules. New antigens are needed and might be identified by activating non-specific responses against lymphoma in vivo. Alternative approaches include using antibodies to block immune regulatory pathways, thereby suppressing tolerance. If new antigens can be found, passive transfer of specific T cells, a technology already developed for persistent viral infection, could be considered. Certainly B-cell tumors bring together biological understanding and clinical application, with effective immunotherapy already in place and cure the goal.

062 IMMUNOTRANSPLANT FOR MANTLE CELL LYMPHOMA: PHASE I/II STUDY PRELIMINARY RESULTS

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Introduction: Mantle cell lymphoma (MCL) has a poor long-term prognosis. Though autologous transplant prolongs survival, novel and mechanistically distinct therapies are needed to target residual, myeloablation-resistant tumor cells that result in relapse. Trials of CpG-based vaccines for low-grade lymphoma have shown induction of anti-tumor T cells and clinical responses [Brody J. et al, JCO 2010]. In a pre-clinical model, we developed the immunotransplant maneuver combining: 1) CpG-based vaccination, 2) harvest of vaccine-primed T cells, 3) myeloablation with stem cell rescue, and 4) T cell re-infusion. Immunotransplant amplifies the proportion of anti-tumor T cells by an order of magnitude and cures even bulky, systemic lymphoma burden [Brody J. et al, Blood 2009].

Methods: We initiated a phase I/II study of immunotransplant for newly diagnosed MCL patients per the schema described. The primary endpoint is anti-tumor immune response; we hypothesize that immunotransplant will amplify anti-tumor T cells as in the pre-clinical model. Anti-tumor T cells are assessed by co-culturing autologous tumor with peripheral blood T cells and measuring their production of effector molecules, such as: IFNg, TNF, IL2, CD137, perforin and granzyme. A secondary endpoint is measurement of molecular residual disease (MRD) using both standard ASO qPCR and high-throughput sequencing of the entire BCR repertoire; the study is powered to detect a 50% improvement in sustained molecular remission rate compared to recent trials of standard transplant [Pott C. et al, Blood. 2010, Geisler C. et al, Blood. 2008].

Results: Accrual has been rapid with 21 patients enrolled in 18 months. Vaccine has been produced for all patients and 13 patients have completed the immunotransplant protocol so far, demonstrating feasibility and safety. To date, all treated patients remain in clinical remission and immune testing has demonstrated immunotransplant-induced amplification of anti-tumor T cells in 83% of patients thus far. Notably, we have observed differing patterns of anti-tumor T cell reactivity amongst these patients, some with primarily CD8 T cell responses, some with CD4 T cell responses, and some with a combination.

Conclusions: Pre-clinically, amplification of anti-tumor T cells correlates with cure of even myeloablation-resistant disease. The reiteration of anti-tumor T cell amplification in our preliminary patient data raises the possibility that immunotransplant may improve clinical outcomes. MRD testing should suggest whether certain patterns of T cell response correlate with clinical benefit and whether the cohort has a better-than-expected molecular remission rate.

063 A PHASE II STUDY OF CT-011, AN ANTI-PD-1 ANTIBODY, AFTER AUSCT IN RECURRENT/REFRACTORY DLBCL: FIRST ANALYSIS OF PROGRESSION-FREE-SURVIVAL (PFS), OVERALL SURVIVAL (OS) AND TOXICITY (TOX)

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Introduction: PD-1 (Program Death-1), an immune inhibitory receptor and its ligand PD-L1 and PD-L2, play a key role in immune suppression and evasion mechanisms, inhibit activation signals and are pro-apoptotic in effector lymphocytes. CT-011, a humanized antibody, blocks PD-1 function, increasing NK and T-cell activity in vitro and in experimental tumors. We hypothesized that CT-011 would delay recurrence in pts with DLBCL after AuSCT.

Materials and Methods: Pts were eligible if they had recurrent/refractory DLBCL, ECOG PS=0,1 and chemo-sensitive disease. N=72 pts and CT -011 was given at 1.5mg/kg x 3 q6wks. The primary endpoint was % of pts who had not relapsed or died at 18 mos after AuSCT. The minimum required 18 mo PFS estimate was 69% to ensure 85% power and 10% type I error.

Results: Median age=57 (19-80), and 39 (54%) had ECOG PS=0, 70 (97%) had prior rituximab, 6 (8%) had radiation post transplant. Pre-transplant 43 (47%) had IPI score of 3-4 and 42(58%) had marrow involvement. Toxicity included 8(11%) gr 3-4 neutropenia and 1(1%) thrombocytopenia. There was no grade 3-4 non-heme tox. At the time of this analysis, 56 pts were followed for at least 18 mos and estimated 18 mo PFS and OS are 69% and 84% respectively (table). These data compare favorably to the Coral study where the estimated PFS and OS at 18 mos was 45% and 57% respectively.

Conclusions: Compared with historical control data, we found that the PFS and PS in pts after AuSCT for recurrent/refractory DLBCL are improved with CT-011. There was acceptable tox and CT-011 was well-tolerated. These data provide the first signal of clinical efficacy of an anti-PD1 antibody in DLBCL and suggest that randomized Phase III trials are warranted.

Outcome	6mo	12mo	18mo
PFS	88	74	69
(95%CI)	(78,94)	(62,83)	(56,78)
OS	96	91	84
(95%CI)	(87,94)	(81,96)	(72,91)

064 PROMISING RESULTS OF AN ANTI-CCR4 ANTIBODY, KW-0761, FOR RELAPSED ADULT T-CELL LEUKEMIA-LYMPHOMA (ATL)

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Introduction: ATL is a distinct T-cell malignancy associated with HTLV-1, carrying a poor prognosis. ATL, as well as other peripheral T-cell lymphomas (PTCLs), is characterized by its cell surface expression of CC chemokine receptor 4 (CCR4), to which KW-0761, a defucosylated, humanized antibody with enhanced ADCC, binds. In a phase I study in patients (pts) with CCR4+ATL and PTCL, encouraging efficacy of KW-0761 (ORR of 31%; 2CRs and 3PRs) was observed (JCO 2010;28:1591). Here, we report the result of a pivotal phase II study of KW-0761 in pts with CCR4+ relapsed ATL.

Methods: A multicenter phase II study of KW-0761 has been conducted for pts with CCR4+, relapsed ATL with the primary endpoint being overall response rate (ORR). Responses of disease lesions, progression-free survival (PFS) or overall survival (OS) was also assessed. Pts were planned to receive 8 weekly intravenous infusions of KW-0761 at 1.0 mg/kg. Objective responses were assessed by an independent efficacy assessment committee.

Results: 28 pts were enrolled, among whom, 27 had at least one infusion of KW-0761. Most observed adverse events (AEs) were mild to moderate in severity. 6 pts had severe AEs of skin including 1 Stevens-Johnson syndrome (G3) and 5 skin rashes (G3), all of which were manageable with steroids. Acute infusion reactions were frequently observed, but mostly tolerable. Among the 26 pts evaluable for efficacy, KW-0761 exhibited an ORR of 50% (13/26; 95% CI, 30 to 70), including 8 CRs and 5 PRs, with response rates in each affected lesion being 100% (13/13) for peripheral blood, 63% (5/8) for skin, and 25% (3/12) for lymph node disease, respectively. Median PFS and OS were 5 and 14 months, respectively. Updated data will be presented at the meeting.

Conclusion: KW-0761 demonstrates definitive activity with acceptable toxicities in pts with CCR4+, relapsed ATL. A multicenter, randomized study of KW-0761 in combination with chemotherapy for untreated ATL pts is ongoing.