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 tumourigenesis 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 tumour cell growth and survival. Amplified 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 unmaturated 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 idiotype (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 tumour 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 is which, 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 activating 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, 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 chemo and in experimental tumors. We hypothesized that CT-011 would delay recurrence in pts with DLBCL after AuSCT.

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

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, 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.

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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.