session 13 – new drugs

132 NEW DRUGS IN MULTIPLE MYELOMA

J.F. San Miguel[1], E. Ocio[1]
[1]Hematología, Hospital Universitario de Salamanca, Salamanca, Spain

The outcome of Multiple Myeloma (MM) patients has significantly improved over the last decade, and this is mainly due to the efficacy of novel drugs, such as Thalidomide, Lenalidomide, and Bortezomib. Nevertheless, most patients relapse and become eventually refractory to all available treatments. Therefore, drugs with novel mechanism of action are urgently needed in order to improve the outcome of relapsed MM patients. The investigation of these novel therapies is currently focusing in agents aiming at specific targets essential for MM emergence and progression. In this sense, some of the molecular events responsible for the transformation of a normal into a malignant Plasma Cell represent potential therapeutic targets. Thus, the t(4;14) translocation induces the constitutive activation of the oncogenic receptor tyrosine kinase (RTK) FGFR3, and several IgH translocations lead to Cyclin D deregulation representing a common pathogenic event in MM. Therefore, the use of inhibitors of cyclin dependent kinases as well as inhibitors of the FGFR3 tyrosine kinase could be attractive therapeutic targets against MM. The second area of MM pathogenesis with important implications for treatment intervention is the interaction between the malignant cell and the bone marrow microenvironment through soluble molecules and membrane receptors. This interaction promotes MM cell growth and proliferation involving different signalling pathways. In this area several targeted oriented drugs are already at early phases of clinical investigation, including: 1. Agents acting against surface receptors present in plasma cells, such as IL6-R, CD56, CS1, or CD40. 2. Agents designed to block RTKs, like, the already mentioned FGFR3, VEGFR; IGF-1R or c-Kit. and 3. Drugs interfering with the activated signalling pathways, including Farnesil Transferase (Tipifarnib), RAF (RAF265), MAPK (SCIO-469), STAT3 (Atiprimod), MTOR (RAD001) or AKT (Perifosine). Other mechanism which has demonstrated to be critical for MM survival is the unfolded protein response (UPR). Three classes of agents have been designed to target this system: Hsp90 inhibitors, novel proteasome inhibitors (NPI-0052 and Carfilzomib) and inhibitors of aggressome formation (tubacin). Finally, epigenetic is emerging as a relevant player in tumor progression, therefore the use of histone deacetylase (HDAC) inhibitors or demethylating agents seems to be promising for the treatment of MM patients. Unfortunately, the expectations raised by some of these agents have not been so far confirmed in the clinic. It is probable that these targeted directed drugs will be more effective in science based combinations with other agents which have already shown clear efficacy in MM.

133 NEW DRUGS FOR B-CELL NON-HODGKIN'S LYMPHOMAS (NHL)

B.D. Cheson[1]
[1]Hematology/Oncology, Georgetown University Hospital, Washington, D.C., United States

Improved outcome for pts with B-NHL, has resulted from safe and effective biological therapies, e.g., rituximab, Y90-ibritumomab tiuxetan and I-131 tositumomab. Unfortunately, follicular NHL and MCL are not curable and almost 40% of diffuse large B-NHL pts fail to respond to initial treatment or relapse. Thus, new treatments are needed. One of the most promising agents is bendamustine, a novel nitrogen mustard and antimetabolite hybrid non-cross-resistant with other alkylating agents. This drug has been extensively used in East Germany for over 40 years with activity in NHL, chronic lymphocytic leukemia, multiple myeloma, and a variety of solid tumors, with an acceptable safety profile. In US trials, over 70% of pts with relapsed/refractory follicular, low grade and MCL respond, including 35% CRs, setting the new standard for drug activity in such patients. The combination of bendamustine with rituximab yields > 90% responses in relapsed patients with indolent histologies or MCL, and the combination is being added to bortezomib. Lenalidomide is more potent than its parent thalidomide in vitro and clinically, with activity in both indolent and aggressive NHL. CALGB is randomizing relapsed follicular NHL pts to lenalidomide alone or with rituximab. A study at Georgetown Hospital is combining bendamustine with lenalidomide. Small molecules directed at the apoptotic pathways include oblimersen sodium, obatoclax, AT-101 (gossypol derivative), APO-2L/TRAIL, ABT-263, and YM155 (anti-survivin). Although their single agent activity is likely to be limited, they enhance the efficacy of chemotherapeutic agents or monoclonal antibodies. Inhibitors of histone deacetylase and mTOR are also active. New monoclonal antibodies include a series of human/humanized anti-CD20s engineered to bind to a novel epitope, enhance ADCC, CDC, CD20 binding, or activation of apoptosis; ofatumumab, IMMU-106, PRO131921, AME-133 and GA101. Others directed at CD40 (SGN-40), CD22 (epratuzumab), CD80 (galiximab) and TRAIL are in clinical trials alone and in combination with rituximab or chemotherapy. Small modular immunopharmaceuticals (SMIPs) also have potential. CALGB pts in low/intermediate FLIPI groups are treated with targeted doublets as initial therapy: first rituximab plus galiximab, currently rituximab plus epratuzumab. Rational development of combinations of these various agents, guided by correlative laboratory science, will increase the cure of pts with B-NHL.

134 NEW DRUGS FOR THE TREATMENT OF T-CELL LYMPHOMA

O.A. O'Connor[1]
[1]Herbert Irving Comprehensive Cancer Center, College of Physicians and Surgeons, The New York Presbyterian Hospital, Columbia University, New York, N.Y., United States

The T-cell lymphomas represent a very heterogeneous and challenging group of hematologic malignancies. Given the rarity of these diseases, there is little to no consensus regarding the management of patients either in the front line or relapsed state. One of the major difficulties with the management of these malignancies is the fact that there have been very few T-cell 'centric' drugs that have found their way into the standard treatment regimens. Most treatments used in T-cell lymphoma have been adopted based on the use of drugs active in the treatment of B-cell lymphomas (i.e. CHOP, ICE based). Over the past few years, there has been a number of major break throughs in the identification of novel targets and agents with activity in T-cell lymphoma. Gemcitabine, a deoxycytidine analogue, has proven to be a very active drug in a variety of T-cell lymphomas including cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL). Another promising small molecule with activity in T-cell lymphoma is pralatrexate, a 10-deazaaminopterin. This drug was designed to have very high affinity for the reduced folate carrier (RFC), and thus is rapidly internalized into malignant tissue. In ongoing clinical trials, this compound has demonstrated an overall response rate of 50% or more in patients with relapsed or refractory disease. In addition, preclinical studies have demonstrated that pralatrexate is synergistic when administered in a schedule dependent manner with gemcitabine. This observation has been extended to ongoing Phase 1 studies of the combination. Another class of drugs with unusual activity in T-cell lymphomas are the histone deacetylase inhibitors. Interestingly, there seems to be a class effect with regard to these compounds. Vorinostat (previously known as SAHA), has been approved for CTCL. Depsipetide, a naturally occurring HDAC inhibitor has demonstrated an overall response rate of about 30% in patients with CTCL and PTCL, with very durable responses despite their chemotherapy refractory nature. At this time, both depsipeptide and PXD, another hydroxamic acid derivative, are both in registration directed phase 2 clinical trails for patients with CTCL. Another agent, LBH589, a potent hydroxamic acid derivative, has similarly demonstrated marked activity in patients with CTCL. It is now clear there are a number of very exciting agents, and promising targets, that offer the opportunity to develop more T-cell centric based treatment programs. As these agents mature in the clinic, there is enormous hope that more effective upfront treatment programs for T-cell lymphomas will emerge in the very near future.

135 ALL B LYMPHOMA SUBTYPE DO NOT SHARE SIMILAR OUTCOME AFTER FRONT-LINE R-CHOP PLUS BORTEZOMIB TREATMENT : A RANDOMIZED PHASE 2 TRIAL FROM THE GROUPE D'ETUDE DES LYMPHOMES DE L'ADULTE (GELA)

N. Mounier[1], V. Ribrag[1], C. Haioun[1], G. Salles[1], J. Golfier[1], M. Ertault[1], C. Ferma[1], J. Briere[1], P. Brice[1], E. De Kerviler[1], C. Gisselbrecht[1]
[1]Institut Universitaire d'Hematologie, Hospital St Louis, GELA, Paris, France

Background: Bortezomib is the first proteasome inhibitor that showed promising activity in hematologic malignancies. In Jan 2005, we initiated a phase II randomized trial to evaluate front-line R-CHOP + bortezomib in various pathological B lymphoma subtypes.

Methods: 6 cycles of standard R-CHOP-21 were planned, pts were randomized between 2 schedules of bortezomib: arm A (d 1, 4, 8, 11), arm B (d 1, 8). For the first 24 pts (step1), bortezomib was administred at 1 mg/m^2 in arm A and 1.3 mg/m^2 in arm B. For the next 24 pts (step2), it was increased at 1.3 mg/m^2 and 1.6 mg/m^2 respectively. Primary endpoint was CR rate after 6 cycles.

Results: 49 pts were included. Sex ratio M/F: 28 /21. Median age : 63 years [32-76]. IPI 2-3: 18 pts. 3 Lymphoplasmocytic, 6 small lymphocyte, 8 MZL, 2 Malt, 11 FL, 3 MCL, 5 FL with histological transformation and 11 DLBC without adverse factor. In arm A, 5/20 pts received less than 90% of scheduled dose of bortezomib (all in step2). In arm B, 7/29 pts (2 step1 and 5 step2). Grade 3-4 thrombopenia occurred in 14%, Grade 3-4 leucopenia in 41 %. Neurological toxicity occurred in 21 pts: grade 2 in 11 (1 arm A, 10 arm B, 9 in step2) and grade 3-4 in 10 (5 arm A, 5 arm B, 9 in step 2). 48 pts were evaluable for response: 40 achieved CR/CRU :18/20 in arm A, 22/28 in arm B. There were 5 PR, 1 SD and 2 PD. 19/21 pts achieved CR in step 1 and 21/27 in step 2. RC/RCu rate were different among pathological subtype: 74% for small cells (14/19), 72% for FL

(8/11), 100% for MCL (3/3) and 94% for large cells (15/16). After 2 year median follow up, OS was 83% and EFS 64%.

Conclusion: R-CHOP+ Bortezomid is an effective regimen with the best CR rates in large and mantle cells lymphoma patients. However, the dose limiting neurotoxicity should be kept in mind for further trials.

136 ORAL PANOBINOSTAT (LBH589), A NOVEL DEACETYLASE INHIBITOR (DACI), DEMONSTRATES CLINICAL ACTIVITY IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA (HL)

A. Spencer[1], D.J. DeAngelo[2], H.M. Prince[3], K.N. Bhalla[4], T. Fischer[5], A. Liu[6], K. Parker[6], M. Jalaluddin[6], J.W. Scott[6], O.G. Ottmann[7]

[1]Clinical Hematology & BMT, Alfred Hospital, Melbourne, Australia, [2]Medical Oncology, Dana-Farber Cancer Institute, Boston, United States, [3]Hematology/Oncology, Peter MacCallum Cancer Center, Melbourne, Australia, [4]Hematology/Oncology, Medical College of Georgia Cancer Center, Augusta, United States, [5]Hematology/Oncology, University of Mainz, Mainz, Germany, [6]Early Clinical Development, Novartis Oncology, Florham Park, United States, [7]Hematology/Oncology, University of Frankfurt, Frankfurt, Germany

Introduction: Panobinostat (LBH589) is a novel cinnamic acid hydroxamate DACi which induces cell death in multiple hematologic tumor cell lines *in vitro* at nanomolar levels and has demonstrated objective responses in CTCL in ongoing clinical trials.

Methods: In an ongoing Phase I trial, panobinostat is administered orally, once/day, on Mon/Wed/Fri (MWF), every week (Arm 1) or every other week (Arm 2), in 28-day cycles, to adult patients (pts) with advanced hematologic malignancies including HL.

Results: To date, 86 pts have been enrolled: 45 pts in Arm 1 at doses of 20, 30, 40, 60, and 80 mg; 41 pts in Arm 2 at doses of 30, 45, 60, and 80 mg. The maximum tolerated dose has not yet been determined for either arm. Four dose-limiting toxicities (DLTs), none in pts with HL, have been reported in Arm 1: G3 fatigue at 40 mg (2 pts) and 60 mg (1 pt); and G3 QT prolongation at 80 mg (1 pt). No DLTs have been reported in Arm 2. To date, 8 pts with relapsed/refractory HL have been enrolled across arms and dose levels: median age 26 yrs (range 16–41), 3 female, 5 male, median 5 prior therapies (range 4–15), all had prior stem cell transplant. Among HL pts, the most common adverse events (AEs) included diarrhea, nausea, thrombocytopenia, and fatigue. Thrombocytopenia was the only G3/4 AE experienced by >1 HL pt (4 pts). The median number of cycles was 5 (range 2–10) with 6 of 8 pts ongoing. Metabolic PR was observed in 6 of 7 HL pts evaluable for PET response.

	Dose (mg)	Best Response by PET	Best Response by CT	Completed Cycles (*ongoing)
Arm 1	30	PR	PR	10*
	30	PR	PD	2 (discontinued–PD)
	40	PR	PR	3*
	40	PR	SD	4*
Arm 2	45	PR	SD	8*
	45	SD	SD	6*
	45	not done	SD	6*
	60	PR	SD	4 (discontinued–PD)

Conclusion: Panobinostat appears to be well tolerated and has shown evidence of activity based on PET and CT studies in pts with HL.

137 ISOTYPE-SELECTIVE HISTONE DEACETYLASE (HDAC) INHIBITOR MGCD0103 DEMONSTRATES CLINICAL ACTIVITY AND SAFETY IN PATIENTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA (HL)

A. Younes[1], J. Kuruvilla[2], B. Pro[1], A. Wedgwood[1], Z. Li[3], M. Drouin[3], T. Patterson[3], R. Ward[4], R.E. Martell[3], R.G. Bociek[5]

[1]Dept. of Lymphoma/Myeloma, MD Anderson Cancer Center, Houston, United States, [2]Dept. of Medical Oncology & Hematology, Princess Margaret Hospital, Toronto, Canada, [3]Drug Development, MethylGene Inc., Montreal, Canada, [4]Clinical Operation, Pharmion Corporation, Boulder, United States, [5]Dept. of Internal Medicine, University of Nebraska Medical Center, Omaha, United States

Background: With no approved post-transplant therapies, HL patients (pts) with relapsed or refractory disease have poor prognosis. MGCD0103 is an oral isotype-selective inhibitor of histone deacetylases (HDACs) with significant preclinical and clinical activity in hematopoietic cancers.

Methods: Open-label, Phase II trial in adults with relapsed/refractory HL (Trial 010); most with prior transplant. Pts received MGCD0103 at 110 or 85 mg 3x per week in 4-week cycles. Plasma Thymus and Activation Regulated Chemokine (TARC) levels were determined by ELISA. Responses were assessed by CT and PET.

Results: 33 pts have been enrolled to date (median age, 31 yrs; range, 19-62 yrs) of which 29 (88%) had prior transplant. Among 23 pts in the 110 mg cohort, 21 were evaluable, of whom 2 (10%) had a complete response (CR) and 6 (29%) had a partial response (PR) for an overall response (OR) rate of 38% (median time to response, 2 cycles). The 2 pts with CR had progression free survival lasting >270 and >420 days with both responses ongoing. One additional pt (5%) had SD >6 cycles. Among 10 pts in the 85 mg cohort, 5 were evaluable for efficacy, all of whom had tumor reductions of ≥30%, including 1 PR and 2 SDs (45% and 49% tumor reduction). Comparison between 85 and 110 mg revealed 20% and 39% of pts respectively with ≥ grade 3 non-hematological toxicities. Decrease in Day 8 plasma TARC levels correlated with clinical response (PR+CR).

Conclusion: MGCD0103 demonstrated significant anti-tumor activity in relapsed/refractory post-transplant HL. The 85 mg dose exhibited meaningful activity and may be better tolerated.

138 PRALATREXATE (PDX) PRODUCES A HIGH AND DURABLE COMPLETE RESPONSE RATE IN PATIENTS WITH CHEMOTHERAPY RESISTANT T-CELL LYMPHOMAS

O.A. O'Connor[1], P. Hamlin[2], C. Moskowitz[2], C. Portlock[2], D. Sarasohn[2], O. Dumetrescu[2], E. Neylon[1], M. Patterson[1], A. Zelenetz[2], M. Saunders[3], P. Cagnoni[3], D. Mould[4], M. Fleisher[2], A. Califano[2], F. Sirotnak[2], S. Horwitz[2]

[1]Hem/Onc, Herbert Irving Comprehensive Cancer Center, New York, United States, [2]Med, MSKCC, NY, United States, [3]N/A, Allos, Westminster, United States, [4]N/A, Projections Research, Phoenixville, United States

Background: PDX is a novel antifol designed to have high affinity for the reduced folate carrier (RFC-1), which enables rapid internalization.

Methods: A Phase I study of PDX was conducted in patients with lymphoma on an every other week (QOW) and weekly (QW) schedule.

Results: Population pharmacokinetic and pharmacodynamic studies of this patient population demonstrated that elevated area under the curve of PDX exposure and elevated methyl malonic acid (MMA) predicted the risk of mucositis. Based on these data, a schedule modification (from high-dose QOW to low dose QW), and intentional lowering of the MMA with folic acid and vitamin B12 were found to abrogate the dose limiting toxicity (DLT) of mucositis. The maximum tolerated dose (MTD) of PDX on a weekly schedule was 30 mg/m^2 weekly (w) x 6 w Q 7 wks. The DLT was primarily thrombocytopenia. A weekly phase 2 study has accrued 24 patients.In total, 56 patients have been treated with PDX (16 on the QOW schedule, 17 on the QW Phase 1). Thirty-one (57%) had some form of TCL.Among the patients with TCL, 1 is too early to judge for response, and 4 experienced toxicity following only 1-2 doses of drug, deemed possibly or unlikely related to study drug. Of 26 patients who completed at least a cycle of therapy, 14 experienced a major remission (overall response rate [ORR] 54%; 9 complete remissions [CR] and 5 partial remission [PR]). Of the 5 PR, 2 were PET negative. The intent-to-treat ORR was 45%. Durable CR have been documented in the following sub-types: acute lymphoblastic, HTLV-1 ATLL, blastic NK/T, ALK (+) anaplastic large cell, PTCL NOS, subcutaneous panniculitis-like, and g,d-subcutaneous panniculitis-like. Most responding patients had disease *refractory* to conventional therapy. These data support the marked activity of PDX in TCL, producing predominantly complete remissions as the major response, the majority of which are durable. A international confirmatory study is underway.