New developments in Hematology and Oncology in 2011

Guangzhou, China. 25-26 December 2011

Edited by Qifa Liu, Yangqiu Li and Delong Liu

Published: 25 April 2012

These abstracts are available online at http://www.jhoonline.org/supplements/5/S1

MEETING ABSTRACTS

A1
Targeted therapy in head/neck and gastric cancers
Chung-Tsen Hsueh
Loma Linda University, Loma Linda, CA 92354, U.S.A
E-mail: chhsueh@llu.edu

The epidermal growth factor receptor (EGFR/HER1) is a member of the erbB family of receptor tyrosine kinase proteins, which also includes HER2, HER3, and HER4. EGFR is almost universally expressed in squamous cell carcinoma of head and neck (SCCHN), and high levels of expression have been correlated with a poor clinical prognosis [1]. Cetuximab, an IgG1 monoclonal antibody against EGFR, has demonstrated improved survival and disease control when used in combination with radiation therapy for the treatment of locally advanced SCCHN, and in combination with platinum-based chemotherapy in recurrent or metastatic SCCHN [2-4]. Additionally, single-agent cetuximab is active and provides good disease control rate and duration in platinum-refractory SCCHN [5]. Comparison of cetuximab versus cisplatin concurrently with radiotherapy is under investigation in patients with human papillomavirus-associated oropharyngeal cancer, who have better prognosis and may benefit from less toxic treatment [6].

Overexpression of HER2 in gastric cancer results in aggressive clinical course and poor prognosis [7]. Trastuzumab, a monoclonal antibody against HER2, exhibits antitumor activity in HER2 overexpressed gastric cancer cells, and enhances effects of chemotherapy in gastric cancer xenograft overexpressing HER2 [8]. The ToGA study screened about 3,800 patients with advanced gastric cancer from 24 countries, and HER2 overexpression was detected in 22% [9]. Higher rates of HER2 overexpression occurred in intestinal and proximal or gastroesophageal junction cancers than in diffuse or distal gastric cancers. In TOGA study, 584 patients with HER2 overexpression were randomized to receive fluoropyrimidine and cisplatin treatment with or without trastuzumab. Patients who received trastuzumab plus chemotherapy achieved longer overall survival (13.8 months vs. 11.1 months, P= 0.0046), longer progression-free survival (6.7 months vs. 5.5 months, P=0.0002), and higher response rates (47% vs. 35%, P=0.0017) than those who received chemotherapy alone. Complete response was noted in 5.4% of patients receiving trastuzumab plus chemotherapy vs. 2.4% in chemotherapy alone. There were no significant differences in the toxicities between these two groups. This study has established a new paradigm using trastuzumab in combination with chemotherapy in patients with advanced gastric cancer overexpressing HER2.

Neoadjuvant treatment is a standard of care for locally advanced esophageal and gastric cancer. We have previously reported a case of pathological complete response after neoadjuvant chemotherapy with trastuzumab-containing regimen in HER2-overexpressing gastric cancer [10]. Incorporating trastuzumab as a part of neoadjuvant therapy in esophageal and gastric adenocarcinoma overexpressing HER2 is currently under active investigation. Radiation Therapy Oncology Group is conducting a phase III neoadjuvant study in patients with HER2-overexpressing esophageal adenocarcinoma to determine if trastuzumab decreases disease-free survival when added to chemoradiotherapy [11]. Other studies conducted in Europe are adding trastuzumab to oxaliplatin-based regimen as perioperative chemotherapy for HER2-overexpressing esophagogastic or gastric adenocarcinoma, and looking for improvement of pathological complete response and disease-free survival [12,13]. Pertuzumab is a monoclonal antibody interfering with HER2 dimerization with other HER receptors such as EGFR, HER3 and HER4. Pertuzumab and trastuzumab bind to HER2 at different sites, and combination of both antibodies leads to stronger inhibition of erbB signaling and greater therapeutic efficacy when combined with docetaxel in breast cancer [14]. Combination of pertuzumab and trastuzumab with platinum-based chemotherapy is currently studied in HER2-overexpressing gastric cancer [15].

References
A2

Utilizing CD30 expression as a rational target for therapy of lymphoma

Won Seog Kim

Division of Hematology-Oncology, Sungkyunkwan Univ. School of Medicine, Samsung Medical Center, Seoul, Korea


Introduction: Rituximab, identified through pivotal lymphoma research, was the first monoclonal antibody approved by the US FDA in 1997. Since the success of rituximab, monoclonal antibodies have been a major focus for development of targeted agents for lymphoma treatment. A major hurdle in the development of a new antibody is finding a new target antigen. CD30 is an attractive therapeutic target antigen, because it has been identified as a marker of Reed–Sternberg cells in Hodgkin lymphoma (HL) [1], it is known to be expressed on anaplastic large cell lymphoma (ALCL), some cases of mediastinal large cell lymphoma, primary effusion lymphoma and multiple myeloma. However, its expression on normal tissues is restricted to a small number of activated B- and T-lymphocytes [2]. Thus, based on its expression pattern, CD30 could be an ideal therapeutic target.

Naked CD30 targeting antibodies and modified/engineered anti-CD30 antibodies: Although CD30 is considered an ideal target, the results from early clinical trials with first-generation naked monoclonal antibodies targeting CD30 have been disappointing. Ibritumomab (MZB-60) is a fully humanized anti-CD30 monoclonal antibody. Of 72 patients with HL or ALCL, clinical responses were observed in 6 (4 complete response [CR] and 2 partial response [PR]) [3]. SGN-30 is a chimeric anti-CD30 monoclonal antibody. In a phase I trial, one CR was reported in a patient with cutaneous ALCL [4]. In a phase II trial for HL or ALCL, 7 responses (2 CR, 5 PR) in patients with ALCL were reported in 79 patients. Unfortunately, there were no responders in the 38 HL patients [5].

XmAb2513 is a modified anti-CD30 antibody with increased binding affinity to the Fc receptor. In vitro data showed more potent and efficacious cell killing than first-generation anti-CD30 monoclonal antibodies XDA-060 and SGN-30. In clinical trials, only phase I data are available. Therefore, the data are insufficient to assess whether the response is better than that with unmodified antibodies [6].

Radioimmun conjugation: Radiation itself is quite an efficient tool for killing lymphoma cells. If a good radiation source, a well-targeted monoclonal antibody and a conjugation technique are available, a radioimmunotherapy agent can be a good option in lymphoma treatment. Already radioimmunocjugations using diverse radionuclides (including $^{131}$I and $^{186}$Re) are being investigated. In a preclinical animal model, the survival of mice was significantly prolonged by treatment with anti-CD30 antibody HeFi-1 coupled to $^{131}$I [7]. The novel anti-CD30 monoclonal antibody K4 conjugated with $^{125}$T (total dose 0.0035–0.99 Gy) was trialed in 22 patients with refractory or relapsed HL. One CR, 5 PRs, and 3 minor responses were achieved. However, 7 patients experienced grade 4 hematologic toxicity 4 to 8 weeks after treatment. Therefore, the development of this drug did not continue [8].

Antibody–drug conjugate: brentuximab–vedotin (SGN-35): Brentuximab–vedotin (SGN-35) is an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E (MMAE), a synthetic tubulin binder. Through binding with CD30, brentuximab–vedotin is internalized. Inside the lysosomes of lymphoma cells, free MMAE is released. Therefore, no immune response is required to achieve efficacy [9]. Two phase I trials with different schedules (treatment every 3 weeks or weekly) have been conducted. In the schedule with treatment every 3 weeks, the maximal tolerated dose was 1.8 mg/kg. Objective responses were observed in 17 of 45 relapsed or refractory CD30-positive hematologic malignancies including HL and ALCL. Of the responders, 11 achieved CR [10]. In a phase II trial with 102 patients with relapse after autologous stem cell transplantation (ASCT), who were treated with 1.8 mg/kg every 3 weeks, the overall response was around 75% (32% CR) with a median duration of response of 6.7 months. In a single arm phase II trial including 58 relapsed systemic AML patients, the overall response was 86% (58% CR), with a median duration of response of 12.6 months. Based on these excellent outcomes, brentuximab–vedotin was approved by the FDA in August 2011. In HL patients, brentuximab–vedotin is indicated after the failure of ASCT or after the failure of at least two prior regimens of combination chemotherapy if the patients are not ASCT candidates. In systemic ALC patients, it is approved after failure of at least one prior multianti antibody chemotherapy.

Overcoming the limitations of anti-CD30 targeting antibodies: Based on its expression patterns, CD30 should be a good therapeutic target. However, it can be shed in a soluble form, resulting in a reduction in the effect of anti-CD30 monoclonal antibodies by competitive binding. Thus, developing a monoclonal antibody targeting membrane-associated CD30 epitopes (Ep2: amino acids 107–131, Ep7 amino acids 222–238) may have potential advantages [11]. Although antibodies have exquisite selectivity for tumor over normal tissue, antibody localization to tumors is inefficient. Diabodies (50–55 kDa) can penetrate tumor more rapidly and accumulate more drug in tumors because they are smaller than IgG (150 kDa). An anti-CD30 diabody–drug conjugate (diabody–ve-F4) showed potent antitumor activity and tolerable toxicity in a mouse model [12].

Future directions: After the early success of anti-CD30 monoclonal antibodies, a variety of clinical trials are ongoing. These antibodies can be combined as a part of first-line treatment, for example, combining ABVD with different levels of SGN-35, as part of salvage combination chemotherapy, maintenance, or as part of a conditioning regimen. After more information is obtained through clinical trials in the near future, new therapeutic strategies can be defined.

References


T-cell immunodeficiency and reconstruction based on TCR rearrangement analysis in hematological malignancy: update from 2011 ASH annual meeting
Yangqiu Li
Institute of Hematology, Medical College, and Key Laboratory for Regenerative Medicine of Ministry of Education, Jinan University, Guangzhou 510632, China
E-mail: yangqiuil@hotmail.com

Introduction: Poor cellular immune function may relate to carcinogenic processes and to worse prognosis in solid tumor patients as well as in leukemia. Moreover, the progression of tumor might further induce the cellular immune suppression. Therefore, a set of molecular immunological techniques to analyze and monitor the changes of host T-cell immune status is needed, which can fully characterize the feature of T-cell immunodeficiency in different malignancies, providing information and direction for immune reconstruction, in particular for enhancement the specific anti-tumor immune function.

The feature of T-cell immunodeficiency in hematological malignancies: In recent years, molecular analysis of the T cell receptor (TCR) utilization feature based on the principle of TCR α, β, γ and δ gene rearrangement and deletion reorganization, has proven to be an effective technique for studying the distribution of T cell repertoire, the diversity of TCR subfamilies [1,2], the antigen specific expansion of T-cell clones and the recent thymic output function [3,4]. This in turn can help to characterize the feature of host T cell immune status, the identification of T-cell populations of interest in cancer, as well as the peripheral immune repertoire reconstitution after hematopoietic stem cell transplantation (HSCT).

T-cell immunodeficiency is a common feature in different hematological malignancies, including the absence of TCR α and β subfamilies, decreased diversity of TCR repertoire, reduced thymic recent output function (naive T cells) and lower frequencies of TCR subfamily naive T cells. An impaired thymic export function and, as a consequence, altered ability to maintain T cell homeostasis may play an important pathogenic role in hematological malignancies. On the other hand, clonally expanded T cells could be identified in some TCR subfamilies in leukemia patients, which display specific anti-leukemia cytotoxicity like WT1 or BCR-ABL specific CTL, indicating that specific anti-leukemic T cells could be generated in vivo. This suggests that the host could have the ability of specific immune response to leukemia associated antigens, despite of T cell immunodeficiency.

T-cell immune reconstitution and establishment of specific anti-tumor and virus immunity: Prolonged period of immunodeficiency and poor immune reconstitution after stem cell transplantation place patients at high risk for viral infection and disease relapse, resulting in significant morbidity and mortality. Reversion of the cellular immunodeficiency is one of the crucial steps for improvement the outcome of tumor therapy in hematological malignancies. Moreover, the T-cell immune reconstitution is a key determinacy of long-term outcome in patients with hematological malignancies post chemotherapy or stem cell transplantation.

T-cell immune reconstruction not only ensures the function recovery of the comprehensive T-cell immunity, a broad TCR repertoire and recent thymic emigrants, more importantly, also the enhancement of the specific anti-tumor cellular immune function, which plays determinant role on elimination of minimal residual disease, relapse prevention and improvement of prognosis in hematological malignancies. Antigen specific T-cell immune reconstitution could be carried out by active (cancer vaccine) or adoptive immunotherapy (T-cells transfusion) [5-8]. Cancer vaccines induce expansion and functional differentiation of tumor antigen-specific effectors and memory cells. The latter are particularly relevant for prevention of disease relapse. Adoptive antigen specific immunotherapy is one of the best approaches for tumor immunotherapy. The antigen specific CTL can directly kill tumor cells, ignoring the host immune status.

Antigen specific CTL could be amplified by cellular or gene engineering techniques. Peptide -specific stimulation in vitro can induce high-affinity CTL (auto- or allogeneic) capable of recognizing tumor cells expressing the appropriate tumor antigen. For example, Epstein-Barr virus (EBV)-specific CTL were used to treat the post transplantation lymphoproliferative disease (PTLD) or EBV+ lymphoma, CMV-specific CTL were used to establish anti-CMV immunity in immunodeficiency patients post allogeneic stem cell transplantation [9,10]. Genetically-modified CTL were obtained by engineering antigen specific TCR gene, thus altering their original antigen specificity and arming them with new cytotoxicity for tumor cells. The approach provides a new strategy for adoptive specific immunotherapy in malignancies and so on. A lot of TCR-modified CTL against different leukemia and lymphoma were developed, like mHagHA-2, EBV, WT1, CML or DLBCL-specific TCR modified CTL [5-8,11,12], as well as the single-chain antibody-derived chimeric antigen receptors (CARs) modified T cells that specifically recognize surface molecules expressed on malignant B cells (CD19) or acute myeloid leukemia cells (CD33) independent from HLA [13,14].

In summary, dynamic detection of the alteration of host immune function in patients is important for the defense of host against neoplastic transformation and so on. The new techniques of tumor immunology, molecular biology and increased knowledge of the optimal methodology for generation of T-cell products and optimization of gene therapy approaches make it possible to enhance the function of adoptively transferred T cells. This enhances tumor- specific response and can reverse the host immunodeficiency status.

References
Recent advances in myelodysplasia: update from 2011 ASH annual meeting

Dellenqi Liu
Division of Hematology /OncoLOGY, New York Medical College & Westchester Medical Center, Valhalla, NY 10595, USA
E-mail: DELLONGLIU@NYMC.EDU
Journal of Hematology & Oncology 2012, 5 Suppl 1

Significant progresses have been made in genetic research in MDS. Through RNA interference technology, knock-down of RIP14 recapitulated the pathological process of decreased erythropoiesis [1]. Transgenic expression of RIP14 in 5q- MDS cells rescued the phenotype of insufficient erythropoiesis. This strongly suggests that haploinsufficiency of RIP14 is one of the molecular mechanisms in the pathogenesis of 5q- MDS. SF3B1 is a core component of RNA spliceosome and involved in the regulation of the mitochondrial pathway. In a study of 533 patients (pts) with MDS, 150 (28.1%) was found to have SF3B1 gene mutation, which has a positive predictive value of 97.7% for RARS and correlates well with better overall survival (OS) and lower risk for AML transformation [2,3]. Hypomethylating therapy represents a significant milestone in myelodysplasia (MDS) management. TET2, IDH1/2, and DNMT3A are regulators of DNA methylation [4]. EZH2 and UTX were found to be involved in the histone H3K26 and H3K27 methylation. ASX1 was found to be deleted in 11-15% of MDS pts. In a study of 88 pts with MDS, mutations of DNMT3A, IDH1/2, and TET2 were found to be correlated with responses to azacitidine (decitabine)/64% in mutated vs 35% wild type, P=0.001) [5], microRNA-21 may also serve as a biomarker for therapy response to hypomethylating agents in MDS. In a study of 63 pts, lower level of serum miR-21 correlated with higher PFS and OS (P=0.003 and 0.001, respectively) [6].

In terms of therapy, azacitidine (75 mg /m2 x 5) was studied in combination with lenalidomide (10 mg x 21) in 36 refractory pts (IPSS=3.15). Overall response rate (ORR) was 71% (CR 40, PR 31) [7]. Azacitidine (75 mg /m2 x 5) was also studied in combination with vorinostat (200 mg TID x 5) in 30 untreated MDS pts with poor clinical status (CR>=1.5, Bilirubin >=2.0). ORR was 30% (CR7) and OS was 7 months in these high-risk pts (expected pre-therapy OS <60 days) [8]. Several novel agents were also reported. Oral decitabine was reported in a phase I bioavailability trial [9]. The oral decitabine has a bioavailability of 3.9 to 14%. Oral doses of 30-240 mg in MDS patients had similar safety profiles to that of the 20 mg /m2 IV administration. RAP-536 was found to promote erythropoiesis in a mouse model through an EPO-independent pathway [10]. IRAK1 is a serine /threonine kinase. miRNA-146a –deficient mice had IRAK1 overexpression and developed MDS-like phenotype. Phosphorylated IRAK1 was higher in MDS patients. A small molecule inhibitor of IRAK1 was studied in cell lines and in MDS sample cells. Increased apoptosis was seen in these cells. Interestingly, IRAK1 inhibitor spared the normal CD34+ cells [11].

Iron chelation therapy is increasingly used in MDS pts, especially when MDS patients are living longer with the current therapies. Retrospective analysis of iron chelation therapy in MDS pts was reported from Italy and Canada [12,13]. However, the efficacy in MDS cannot be clearly ascertainated since there is no randomized prospective study specifically addressing this issue.

References
Newly Diagnosed Myelodysplastic Syndrome (MDS) or Acute Myelogenous Leukemia (AML) Not Eligible for Clinical Trials Because Poor Performance and Presence of Other Comorbidities. ASH Annual Meeting Abstracts 2011, 118(21):608.


A5 Restoration of T cell tolerance in primary ITP

Xin-guang Liu, Jun Peng, Ming Hou

Department of Hematology, Qilu Hospital, Shandong University, 107 West Weihua Road, Jining, P. R. China


Primary immune thrombocytopenia (ITP) has been traditionally thought as an antibody-mediated autoimmune disease involving platelet destruction by macrophages in the reticuloendothelial system. More recently it has become obvious that ITP is a more complex disorder in which T cell mediated immunity plays important roles in platelet destruction. Antiplatelet autoantibody production is under the control of platelet-specific helper T-cells, and loss of tolerance to self antigen by T cells is the critical step of the immune dysregulation in ITP. Dendritic cells (DCs) from ITP patients showed enhanced capacity in stimulating autologous T-cell proliferation in the presence of autologous/autoaggenic platelets [1, and ITP patients' T-cells had elevated IL-2 secretion ability compared with controls [2,3], suggesting increased antiplatelet T-cell reactivity in ITP. The epitopes that recognize platelet glycoprotein (GP) IIa on T helper (Th) cells has been determined and mapped by several groups [4,5], thus shedding new lights on the “therapeutic vaccination” approach to reintegrate tolerance in ITP. Autoreactive T-cell reactivity against platelet antigen in active ITP patients has been observed at polyclonal as well as oligoclonal levels [6,7]. Our group has demonstrated that blocking the B7-CD28 interaction with CTLA4-Ig/CsA could induce platelet-specific T cell anergy, which could exert suppressive effect on GP-reactive T cells via inducing tolerogenic dendritic cells (DCs) [8,9]. It has been well established that apoptotic genes, such as Fas, A20, Bax, Calpastatin, IL2RB, were expressed aberrant in patients with active ITP [10,11], leading to autoreactive T-cells resistant to activation induced cell death (AICD), which could in turn support the expansion of self-reactive T-cell clones. A loss of resistance to AICD might be a critical step of the immune dysregulation in ITP. Dendritic cells (DCs) [26], thus providing a clue to the potential of producing antigen-specific Tregs from the patients in vitro for the purpose of antigen-targeted cellular immunotherapy. In conclusion, induction of T-cell tolerance may provide a useful strategy for the management of ITP.

References


A6

Overcoming Gleevec-resistance by blocking oncogene addiction in malignant hematologic cells
Jingjuan Pan
Department of Pathophysiology, Zhongshan School of Medicine, Sun Yat-sen University, 74 Zhongshan Road II, Guangzhou 510089, People’s Republic of China
E-mail: panjx2@mail.sysu.edu.cn

In some types of tumors, malignant cells are highly dependent on the constitutive activation of a certain protein encoded by oncogene, despite existence of additional carcinogenic genetic changes. This phenomenon is referred to oncogene addiction. Typical examples include cyttoplasmic tyrosine kinase Bcr-Abl in chronic myeloid leukemia (CML), receptor tyrosine kinase Bcr-Abl in chronic myeloid leukemia (CML), receptor tyrosine kinase in systemic mastocytosis and gastrointestinal stromal tumors (GISTs), and PDGFRα in hypereosinophilic syndrome (HES). In 2001, the approval of Gleevec (STIS71, imatinib mesylate, Novartis) by FDA (Food and Drug Administration, USA) initiated a revolutionary targeted therapy against cancer with small molecule tyrosine kinase inhibitors. Gleevec blocks the signaling pathway of tyrosine kinase by competitively occupying the ATP-binding pocket of Bcr-Abl, KIT and PDGFRα, and therefore kills these oncogene-addicted tumor cells. Patients with CML and HES have gained much better prognosis with the use of Gleevec.

Acquired point mutations within the target genes (Bcr-Abl, KIT and PDGFRα) is a major mechanism of resistance to Gleevec in some patients with hematologic malignance. The mutations are believed to block the binding of Gleevec to ATP binding pockets of these tyrosine kinases. In this case, novel tyrosine kinase inhibitor such as nilotinib and dasatinib (also called the second-generation of tyrosine kinase inhibitor) have shown been activity against Gleevec-resistant patients bearing some point mutations but the “gate-keeper” mutations (e.g., T315I Bcr-Abl, T674I PDGFRα). Therefore, development of more novel small molecule tyrosine kinase inhibitors is still needed.

This talk covered the advances in the field of overcoming Gleevec resistance in terms of novel compounds and strategies. Pan J et al reported that EXEL-0862 is effective against Gleevec-resistant D816V KIT and T674I PDGFRα (2007). Recently, in vitro and animal data supported that several novel tyrosine kinase inhibitors including (but not limited) AP24534 (ponatinib) and DCC-2036 have been demonstrated effective against T315I Bcr-Abl. However, the efficacy and safety of these compounds (EXEL-0862, AP24534 and DCC-2036) in patients remains to be defined. An alternative approach for overcoming Gleevec-resistance is to decrease the expression of “addicted” oncogenes, which are driving forces of the tumor cells, to kill the malignant cells. Our group discovered several compounds which are effective against Gleevec-resistant tumor cells regardless of resistance to imatinib. The compounds kill cells harboring gate-keeper mutations of tyrosine kinases by lowering the expression of the oncogenes (Bcr-Abl, KIT and PDGFRα). Examples include triptolide, pristimerin and SNS-032 (transcription inhibitors), homoharringtonine (a translation inhibitor), and celastrol (a hsps90 inhibitor). In summary, Gleevec-resistance remains a challenge in leukemia. The findings from us and others suggest that several aforementioned compounds are promising agents to overcome Gleevec resistance, and warrant clinical trials.

A7

Targeting p53 by small molecule p53 activators in multiple myeloma
Mananjendra N Saha, Yijun Yang, Hong Chang
Dept. of Laboratory Hematology, University Health Network, Dept. of Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Canada
E-mail: Hong.Chang@uhn.toronto.ca

For the past three decades of research, p53 has been identified as one of the most targetable molecules for developing anticancer treatments. This tumor suppressor protein is involved in apoptosis, cell cycle arrest and senescence. Impairment of p53 function in tumors occurs either as a result of mutations in the TP53 gene itself or the abrogation of signaling pathways regulating p53 that are required to exert its cellular function [1]. MDM2 is a transcriptional target of p53, which creates an important negative feedback loop that controls the activity of p53 in response to stress. The MDM2 E3 ubiquitin ligase tightly regulates p53 by targeting it for ubiquitin-dependent proteasomal degradation [2]. In experimental models, disrupting the MDM2–p53 interaction restored p53 function and sensitized tumors to chemotherapy or radiotherapy. This strategy could be particularly beneficial in treating cancers that rarely harbor TP53 mutations/deletions; for example, hematologic malignancies such as multiple myeloma (MM), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and acute myeloid leukemia (AML) [1,3]. The most well studied small-molecule inhibitor of the MDM2–p53 complex is nutlin. Nutlins are a group of cis-imidazoline analogs that have a high binding potency and selectivity for MDM2 and are being tested in phase I clinical trials in patients with hematologic neoplasms and advanced solid tumors [4]. p53-mediated effects of nutlin, such as induction of cell cycle arrest and/or apoptosis, have been demonstrated in cancers characterized by non-mutated TP53, including B-CLL, AML, and ALL [1]. Moreover, it can inhibit tumor growth in a non-genotoxic manner in xenografted tumor mice [1]. We have provided the evidence that nutlin mediated apoptosis can be mediated by both extrinsic and intrinsic pathways. Importantly, our study demonstrated that nutlin can utilize both p53-transcription-dependent and transcription-independent mechanisms to trigger p53-mediated apoptosis suggesting that transcriptional and mitochondrial functions of p53 are equally important for nutlin-triggered apoptosis in MM cells [5].

Another activator of the p53 pathway is the small molecule RITA (reactivation of p53 and induction of tumor cell apoptosis) which is not yet in clinical trials. RITA acts differently to the nutlins by binding directly to its proposed p53 (rather than MDM2) binding site and blocking its ability to interact with MDM2 [6]. However, there appears other mechanisms by which RITA increases p53 activity in cells, since there is
In addition, we also demonstrated that RITA inhibits multiple myeloma cell growth through induction of p53-mediated caspase-dependent apoptotic signaling in MM. Our studies underscore the tremendous potential of these two small molecules for enhancing our understanding of the intricate complexities of the p53 pathway by small molecule antagonists of MDM2. Furthermore, our study reveals that special EBV-associated disease in CNS and pulmonary had been observed in normal cells [8]. More recently, our study shows that RITA induced p53-dependent apoptosis of MM cells is mediated by targeting JNK or its upstream targets. Both genetic and pharmacological inhibition of JNK activation resulted in inhibition of activation of p53 and induction of apoptosis by RITA [9]. Moreover, RITA shows preclinical activity for retardation of tumor growth and prolongation of survival in MM mice xenograft models. In addition, we also demonstrated potential synergistic cytotoxic responses of RITA in combination with nutlin [8] or with the JNK activators dexamethasone or 2-Cyano-3,12-dioxooleana-1,9-dien-28-oic Acid (CDDO) [9]; or of nutlin in combination with velcade, a proteasome inhibitor [10]. Our results indicated a novel mechanism for RITA in JNK signaling and p53-mediated apoptosis in MM cells and provided a preclinical framework for evaluating RITA in clinical trials for the treatment of MM.

Our studies underscore the tremendous potential of these two small molecules for enhancing our understanding of the intricate complexities between different networks of cell death as well as for therapeutic induction of apoptosis in myeloma cells. Further, nutlin or RITA in combination with other available therapeutic agents and also as single agents present a promising novel approach for p53-targeted therapies of MM, which warrants further exploitation.

References

Epstein - Barr virus - associated Diseases in Allogeneic Hematopoietic Stem Cell Transplantation

Xiu-Il Wu, Qi-Fa Liu
Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou Dadao North Street NO.1838, Guangzhou 510515, Guangdong, China
E-mail: liuqf6a28@163.com

Epstein - Barr virus (EBV) is a gammaherpesvirus that infects more than 90% of humans. Most EBV primary infections and reactivations are subclinical and require no therapy in immunocompetent people. However, EBV infection or reactivation may result in life-threatening diseases in immunocompromised people [1-5]. EBV infection and reactivation might be associated with a spectrum of clinical presentations ranging from fever to post-transplant lymphoproliferative diseases (PTLD), including viremia, pneumonia, encephalitis/myelitis, PTLD, and so on, in recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT), which arise as a consequence of infected T/B lymphocytes, epithelial cells and neural cells, and they are sustained by EBV latency products [2,3,5]. EBV-associated PTLD were only the tip of the iceberg of post-transplant EBV-associated diseases [2], but this is short of large sample data to establish the incidence of EBV-associated other diseases other than PTLD in recipients of transplants. Kinch et al reported that 7 of 16 patients with EBV-DNAemia developed EBV-associated diseases in 39 recipients of allo-HSCT, including 3 PTLD, 1 myelitis, 1 encephalitis and 2 reactivations with fever [7]. In one of our prospective study, 16 of 64 patients with EBV-DNAemia developed PTLD and 11 patients developed EBV-associated other diseases, including 6 fever, 1 encephalitis, 1 myelitis, 1 pneumonia, 1 encephalitis accompanying pneumonia and 1 enteritis accompanying hepatitis, in 172 recipients of allo-HSCT. The incidence of PTLD in a large study varied from 0.5% to 22% after allo-HSCT, depending on the number of risk factors including T-depleted graft, the use of ATG, unrelated donor, HLA - nonmatched, acute / chronic graft versus host disease (GVHD), cytomegavirus (CMV) antigen-emia, and so on [3,8,9]. Except for lymph nodes, EBV can also involve nearly all other tissues and organs in recipients of transplants, and isolated central nervous system (CNS) involvement with PTLD is considered to be an exceedingly rare complication after allo-HSCT [10]. But our prospective study showed that 16 of 27 patients with EBV-associated diseases were extranodal involvement and 12 patients developed EBV-associated CNS diseases (6 CNS-PTLD, 5 encephalitis and 1 myelitis).

According to the data of the European Group for Blood and Marrow Transplantation (EBMT) [11], RQ-PCR monitoring of EBV-DNA of blood in 73% transplant center has become a routine method for identifying HSCT recipients at risk for developing EBV-associated disease, diagnosis, preemptive therapy and therapeutic evaluation. EBV-DNA loads of blood are acted as the main basis for diagnosis, preemptive therapy and therapeutic evaluation, but our study and others cases reports [12,13] showed that special EBV-associated disease in CNS and pulmonary had the discrepancy in EBV-DNA loads; sometimes repeated testing with real-time PCR in peripheral blood failed to show any evidence of EBV reactivation, and the change of EBV-DNA loads of blood was inconsistent with disease development. But frequent quantitative monitoring of EBV viral load in high-risk patients is still important to prevent occurrence of EBV-PTLD [14].

Important issues of low morbidity and mortality of EBV-associated disease is restoring the immune response to EBV. Therefore, one of prevention and therapeutic option is to manipulate the immune system to prevent and eradicate these malignancies. In recipients of allo-HSCT in particular, these strategies aim to tilt the balance toward EBV immune responses either by depleting the B-cell population (including EBV-infected B cells) or by augmenting the cellular immune response to EBV. The patients with high risk EBV-DNA-emia are advocated to perform preemptive therapy, rituximab (anti-CD20) has been applied widely as first-line drug of preemptive therapy. The treatment of EBV-associated diseases include rituximab (AII), reducing immunosuppression (BII), donor lymphocyte infusions (DLI) (CII) and donor EBV-specific cytotoxic T cells (CTL) infusion (CII), and chemotherapy (CIII). Antiviral agents (EIII) and intravenous immune globulin (IGIV) (DIII) are not recommended for PTLD [5]. Rituximab has dramatically decreased EBV-PTLD incidence and leads to better overall survival [15-18]. The initial rate responses of administration of rituximab to EBV-associated diseases ranged from 39.2% to 100% [5,17,19]. But recently report indicated rituximab preemptive treatment was associated with high infection rate and prolonged immune defect [15]. Reducing immunosuppression to restore immune responses to EBV is the not a useful approach for treating EBV-associated PTLD after allo-HSCT, because the patients are profoundly immunosuppressed and the regenerating immune system usually cannot recover fast enough to eradicate the malignant cells, and meanwhile, high risk of occurrence of GVHD exists. EBV-specific CTL acts as the best treatment for EBV-associated diseases [20], but this approach is currently confined to experimental protocols, and additional drawbacks are the time (2-3...
months) and facilities required for CTL production. Other therapeutic strategies such as DLI, chemotherapy, or use of antiviral agents have a limited place in the management of PTLD.

In conclusion, EBV infection or reactivation can present as a variety of clinical symptoms and signs, and involve nearly all tissues and organs in recipients of allo-HSCT. EBV-associated other diseases (other than PTLD), especially CNS and pulmonary diseases, were not rare in recipients of allo-HSCT. EBV-DNA monitoring of blood was a routine method for diagnosis of PTLD and acted as an important indicator for preemptive therapy and therapeutic evaluation. However, case reports demonstrated that patients with isolated EBV-associated CNS PTLD might be the cerebrospinal fluid (CSF) EBV-DNA positive, but blood EBV-DNA negative. The preemptive use of rituximab can reduce the risk of death due to EBV-PTLD in the setting of allo-HSCT. The question of over-treatment can be raised and further studies are needed to select candidates for preemptive treatment in order to avoid systematic anti-CD20 treatment and its later potential complications. The problem in developing a treatment for EBV-associated PTLD is the lack of later-phase trials from which to develop evidence-based guidelines. Hopefully, as newer targeted therapies, such as allogeneic EBV-CTL, and more targeted chemotherapy regimens are evaluated, more definitive trials to treat EBV lymphoproliferations will be designed and completed.

References
