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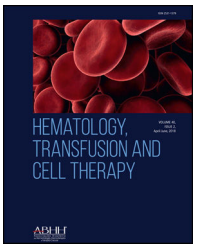

SPEAKER PRESENTATIONS

SP01

TIM-3/Gal-9 signaling is the molecular target for human myeloid leukemia treatment

Koichi Akashi

Acute myeloid leukemia (AML) originates from self-renewing leukemic stem cells (LSCs), an ultimate therapeutic target. The T-cell immunoglobulin mucin-3 (TIM-3) is expressed on the surface of LSCs in most AML patients. We have reported that targeting TIM-3 by anti-TIM-3 monoclonal antibodies could eradicate human AML LSCs in vivo by utilizing xenograft models (Cell Stem Cell, 2011). We then tested the role of TIM-3 signaling evoked by its ligand, galectin-9 (Gal-9), and found that TIM-3+ AML cells secreted Gal-9 into sera, and the ligation of TIM-3 by serum galectin-9 positively regulate the self-renewal capacity of TIM-3+ LSCs through activating the beta-catenin pathway (Cell Stem Cell, 2015). Furthermore, this TIM-3/Gal-9 "autocrine stimulatory loop" is involved in development of LSCs from preleukemic status, including myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN); frequencies of TIM-3+ cells progressively increased and accumulate driver mutations along with disease progression from early/chronic phase to overt leukemia. Thus, signaling molecules downstream of TIM-3 as well as surface TIM-3 itself might be good target to regulate transformation from preleukemic status.

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SP 02

Development of novel therapies in MDS

Kinuko Mitani

Myelodysplastic syndrome (MDS) is one of the bone marrow failure syndromes that usually develop for the elderly. Ineffective hematopoiesis and abnormal morphology are specific characters of the disease. MDS is a hematopoietic stem cell neoplasm caused by gene mutation. About half of the patients transform to acute myelogenous leukemia (AML). Although stem cell transplant (SCT) is the sole curable treatment, cytokine, molecular and immune therapies have been and are being developed to improve survival and QOL of the patients.

Technical progresses in genomic analysis have brought us large amounts of findings regarding molecular pathogenesis in MDS. Gene mutations found in MDS patients are classified into five groups, genes regulating epigenetics, RNA splicing, transcription and signal transduction, and others including *TP53*, *NPM1*, *BCOR*. Through accumulation of these mutations, MDS develops and progresses to AML. Among them, Splicing gene mutations are rather specific to MDS and one of them, *SF3B1* gene mutation, has been employed to sub-classify MDS in the revised 4th version of WHO classification 2017.

When we consider the treatment of MDS patients, we divide them into two risk groups, low and high, according to IPSS and IPSS-R. Supportive therapies for bone marrow failure are employed for low-risk patients, while SCT as a curable therapy or hypomethylating agents (HMAs) aimed at prolonging life are selected for high-risk patients. Supportive therapy includes cytokine therapy such as darbepoietin α and G-CSF, lenalidomide for 5q- patients, immunosuppressive therapy for borderline patients with aplastic anemia, and azacytidine (AZA). Luspatercept inhibits exaggerated TGF-β signaling that underlies a molecular basis on ineffective hematopoiesis. The Medalist trial showed that Luspatercept is especially effective for patients with MDS-RS and/or *SF3B1* mutation. Major part of MDS patients are old and ineligible for SCT, even if they belong to high risk group. For such patients, HMAs (azacytidine and decitabine) that elongate overall survival and time to leukemic transformation are the first-line therapy. Oral AZA (CC-486 and ASTX727) and guadecitabine, and combinations of HMAs with pevonedistat and venetclax are under development. Further, combination of HMA with checkpoint inhibitors such as nivolumab and ipilimumab is promising especially for therapy-naïve patients.

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SP 03

Risk scores and risk factors in CML, are they helpful?

Tomasz Sacha

There are multiple risk scores developed in the last decades to describe entry disease characteristics, enable risk stratification, and predict the clinical outcome of chronic myeloid leukemia (CML) therapy. The treatment-free remission is a new goal of CML therapy postulated and defined also by recent ELN recommendations. In this context, early predictors of good response and chance to reach this ambitious goal are of special interest. The importance of Sokal, EURO (Hasford), EUTOS, and ELTS scores will be discussed. The other risk factors such as additional chromosomal aberrations, additional genetic mutations, BCR/ABL1 transcript type, the dynamics of early BCR/ABL1 transcript decline, the presence of ABL1 KD mutations, and the quality of molecular response could have an important role in planning the optimal treatment. In the era of tyrosine kinase inhibitors and many possible choices, the analysis of risk factors could be considered as a key factor in the decision-making process. This will be discussed during the presentation.

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SP 04

Minimal residual disease detection in multiple myeloma: methods and prognostic significance

Evangelos Terpos

The novel response criteria in antimyeloma therapy, published by the International Myeloma Working Group (IMWG), include minimal residual disease (MRD) assessment in multiple myeloma (MM), aiming to identify better definitions of complete response (CR) than those traditionally defined by conventional methods. IMWG has defined new response categories including (i) marrow MRD negativity with the use of next generation flow cytometry (NGFC) or next generation gene sequencing (NGS), with a cut-off value of 10^{-5}; (ii) imaging MRD negativity using PET/CT; and (iii) sustained MRD negativity (marrow and imaging MRD negativity that remains for 12 months).

The sensitivity of NGS seems to be similar than that of NGF and can be used for detection of rare residual myeloma BM cells at the level of 10^{-6}. However, an advantage of NGS is that it can be applied retrospectively on stored material including not only cryopreserved cells but also archival BM slides. On the other hand, the most commonly utilized NGS-based ClonoSEQ (Adaptive Biotechnologies) platform for MRD evaluation has high cost and requires specialized centers for sample preparation and data interpretation, which, in its current form, makes it challenging for daily clinical management. The major advantage of NGF is its high applicability in 99% of MM patients and the relatively simple manual set-up in diagnostic labs equipped with the appropriate 8-color cytometers, following the standardized EuroFlow guidelines. The cost of the technique is significantly more affordable and the results may be available within a few hours upon BM aspiration. There is no need for a prior diagnostic sample evaluation due to the elegantly elaborated 8-color marker combinations that can efficiently discriminate between normal and aberrant plasma cells in the whole spectrum of intra-phenotypic heterogeneity. Furthermore, NGF methodology allows for an intra-quality control check for hemodiluted samples – the major pitfall for both NGF and NGS approaches- by identifying cellular components (i.e., mast cells, B cell precursors, erythroblasts) that are mainly present in the BM. This point is commonly underestimated, though it consists one of the major advantages of NGF; the multiparametric panels allow for the global characterization of BM cells.

There is no doubt that the achievement of MRD negativity confers a more favorable outcome for treated MM patients. The first meta-analysis by Landgren et al in 2016 and the one that followed by Munshi et al in 2017 have verified the prognostic impact of MRD negativity in the clinical outcome. The latter meta-analysis showed a 59% reduced risk of progression and 43% reduced risk of death for MRD negative patients with a median PFS of 54 months vs. 26 months and a median OS of 98 months vs. 82 months for MRD negative vs. MRD positive patients respectively.

When compared with other prognostic factors, MRD has been shown to be superior and the most relevant predictor of clinical outcome. In multivariate analyses, the achievement of MRD negativity is proven to be the strongest independent prognostic factor which surpasses other favorable prognostic parameters. Patients with high-risk baseline cytogenetics who achieved MRD negativity after treatment, had significantly improved outcomes when compared with MRD persistent counterpart, but most importantly, they experienced similar survival outcomes with standard-risk patients who also achieved MRD negativity. It is important to stress that the favorable prognostication of MRD negativity stands independent of the assigned treatment.

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SP 05

Treatment of relapsed, refractory multiple myeloma: focus on new drugs

Angelo Maiolino

In recent years several new drugs were approved for multiple myeloma (MM) treatment. Three classes are included in almost all lines of MM treatment: proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), immunomodulators (thalidomide, lenalidomide, and pomalidomide) and monoclonal antibodies (daratumumab and elotuzumab) in different combinations.[1] In a relapsed setting, the decision about the new line of treatment should consider patient's related factors and previous MM treatment. Age, frailty, cytogenetics risk, and performance status at relapse have to be analyzed combined with the relapse aggressiveness, exposition to prior therapies, and the history of disease's responses.[2] Patients previously unexposed or those not refractory to lenalidomide, have better outcomes with a triple combination of lenalidomide and

dexamethasone plus daratumumab (POLLUX TRIAL),[3] carfilzomib (ASPIRE TRIAL),[4] ixazomib (TOURMALINE TRIAL),[5] or elotuzumab (ELOQUENT TRIAL).[6] In all these trials, results confirmed that triplet regimens were superior in response rate and progression-free survival. If the patient is considered refractory to lenalidomide, a proteasome inhibitör combination is a standard for treatment in early relapse. Carfilzomib plus dexamethasone was compared to bortezomib and dexamethasone in the Endeavor study and demonstrated superiority in progression-free survival (PFS) and overall survival (OS).[7] Carfilzomib + dexamethasone (KD) combination was recently compared as a control arm versus daratumumab plus KD (Candor Trial).[8] In this phase[3] trial, a superiority in PFS was demonstrated for the triple combination. Daratumumab, bortezomib, dexamethasone combination (Castor Trial)[9] and pomalidomide, bortezomib, dexamethasone (OPTIMISMM)[10] are also good options for this subset of patients, previously exposed and refractory to lenalidomide. Both trials demonstrated superiority in response rate and PFS. New clinical trials are addressing innovative strategies, particularly with belantamab mafodotin, an anti-BCMA antibody, and with anti-BCMA – CAR T-cell. Both demonstrated high efficacy in terms of response rate in Phase1/2 Trials, including heavily pretreated and Penta-refractory patients.[11,12] Large phase 3 trials are planned for hopefully incorporate these strategies to MM treatment.

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SP 06

Current therapy for indolent lymphomas

Guilherme Duffles Amarante[1,2], Marcia Torresan Delamain[3], Carmino Antonio De Souza[3,*]

[1] *Hematology Service, Instituto do Cancer do Estado de São Paulo, Universidade de São Paulo, São Paulo, SP, Brazil*
[2] *Oncologia D'Or, Rede D'Or São Luiz, São Paulo, SP, Brazil*
[3] *Hematology and Blood Transfusion Center, University of Campinas (UNICAMP), Campinas, SP, Brazil*

Introduction: Indolent lymphomas are neoplasms of the mature B-cell that have the survival measure in years even without direct treatment. This group contains follicular lymphoma, lymphoplasmacytic lymphoma and marginal zone lymphoma. Mantle cell lymphoma, although can have an indolent course, it's not included here.

Follicular lymphoma (FL): FL is the second in prevalence between non-Hodgkin's lymphomas (NHL) and the most common with an indolent presentation.[1] Patients can have a heterogeneous evolution, from asymptomatic disease without need for therapy until an aggressive course with poor chemotherapy response. The latter tends to belong in a group of progressive disease within two years of first therapy (POD24).[2] Although a better knowledge of the disease biology, there are current no clear prognostic system that can separate patients in need for aggressive treatment versus those with no need for treatment at all. But it is considered standard only treat patients with high tumor burden or symptomatic. Generally, patients that do need therapy receive CHOP/CVP or Bendamustine with additional anti-CD20 antibody. There seems to be a favorable group that can be treated with Rituximab monotherapy and remain without need for new treatment for a long period.[3] After the GALLIUM trial,[4] where Obinutuzumab was associated with 34% reduction in progression versus Rituximab, this novel anti-CD20 antibody became an option. Although a progression-free survival (PFS) benefit was demonstrated, there was no gain in overall survival (OS) at this point. Maintenance with Rituximab or Obinutuzumab is generally recommended (every 2 months for 2 years), with long term follow up from the PRIMA trial showing a sustained difference in PFS.[5] However, no OS superiority was observed. To reduce toxicity while maintaining efficacy, Lenalidomide plus Rituximab regimen was tested in untreated FL patients ("R^{2}").[6] This "chemo-free" protocol had an equal

PFS rate at 3 years compared with Rituximab plus Chemotherapy, with less hematological toxicity and neutropenic fever. The combination was also effective in the relapse setting, with a median of 40 months in PFS.[7] Chimeric antigen receptor-modified T cells (CAR-T) against CD19 is becoming widely use in lymphoma and has showed efficacy in relapse/refractory FL patients, with report of high complete remission rate and sustained remissions.[8]

Lymphoplasmacytic lymphoma (LPL): LPL is a lymphoma characterize by lymphoplasmacytic cells that produces monoclonal protein (IgM) and infiltrate the bone marrow and lymph nodes. When there is a measure IgM monoclonal production, LPL is a synonymous of Waldenström macroglobulinemia (WM). The *MYD88* L265P mutation occurs in over 90% of cases,[9] serving as a strong diagnostic marker (although not specific of WM). This mutation also has a prognostic role, with patients with the wild type showing a worse prognosis.[10] *CXCR4* is another frequent and important mutation (prevalence of 30% in WM), that together with *MYD88* can guide the treatment choice.[11] WM is an incurable disease of normally elderly patients and the treatment, when needed, focus on achieving a response (rarely complete remission) while maintaining low toxicity.[12] DRC is an option for low tumor burden and more frail patients that do not need urgent treatment. BDR serves well patients for patients with cytopenias and no neuropathy, while BR maybe prefer in bulky disease with high tumor burden.[13] Ibrutinib with or without rituximab can be used in first line[14] or relapsed patients,[15] especially with the *MYD88* mutation. Acalabrutinib and Venetoclax are other new options, with the last as one of the few active treatments in patient's refractory to ibrutinib.[16]

Marginal Zone B-cell lymphomas (MZL): The marginal zone B-cell lymphomas (MZLs) comprise extra nodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), splenic MZL (SMZL) with or without villous lymphocytes and nodal MZL (NMZL) with or without monocytoid B cells. These are three distinct clinical entities with specific diagnostic criteria, clinical and therapeutic implications.[17]

Regarding to localize H. pylori-positive gastric MZL, the initial treatment should be H. pylori eradication. This treatment can induce lymphoma regression and long-term clinical disease control in the most of 50% of the patients.[18] In patients who do not achieve lymphoma regression following antibiotic therapy, irradiation and systemic oncological therapies should be used, depending on the stage of disease. Patients who require systemic treatment, chemotherapy, immunotherapy or both are all effective.[19] SMZL in asymptomatic patients, watch-and-wait is recommended and splenectomy is considered as the recommended first treatment. Rituximab therapy alone can be indicated and has an important response rate with minimal toxicity, particular useful in patients with autoimmune disorders.[20] For asymptomatic patient diagnosed with NMZL is also recommended only observation. If systemic treatment is indicated, chemo-immunotherapy can be performed.[21]

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SP 07

Bone marrow failure

Rodrigo T. Calado

Aplastic anemia may be the result of the immune attack against hematopoietic stem and progenitor cells or the impairment of appropriate hematopoietic stem cell function due to inherited genetic defects. Although bone marrow transplantation is the preferential therapy for severe cases, the majority of patients lack a suitable sibling donor. The thrombopoietin receptor agonist eltrombopag has been recently added to immunosuppressive therapy, reaching high response rates and overall survival, rivaling matched-donor transplant results. Additionally, genetic defects in telomere-maintenance genes appear to be the most prevalence etiology of inherited aplastic anemia. Sex hormones may recover hematopoiesis in these cases. The occurrence of somatic genetic mutations in immune and inherited aplastic anemia may help to understand the complex dynamics of hematopoietic stem cells in vivo.

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SP 08

Immunocompromised patients: prevention, diagnosis and therapy of infection

Marcio Nucci

Patients with bone marrow failure are at increased risk to develop severe infection. The main immunodeficiency is neutropenia, particularly in patients with acute leukemia and severe aplastic anemia. In addition, treatment-related immunodefficiencies further increase the risk of infection, including mucositis caused by intensive chemotherapy, and T-cell immunodeficiency that follows immunosuppressive therapies for aplastic anemia. In neutropenic patients, prophylactic strategies focus on the prevention of bacterial and fungal infections. A key element in the management is the prompt initiation of empiric antibiotic therapy in febrile neutropenic patients, focusing on Gram-negative bacteria. With this regard, the emergence infection caused by multi-drug resistant Gram-negative bacteria is a major challenge, because inappropriate antibiotic coverage is associated with high mortality rates. Therefore, it is imperative to know local epidemiology in order to select the most appropriate antibiotic regimen. Likewise, changes in the initial empiric antibiotic regimen should be driven by objective parameters and not just fever. For invasive fungal disease, while the empiric antifungal therapy is still used, this strategy has been replaced by a preemptive diagnostic-driven approach. In this strategy, serial (2–3×/week) serum galactomannan and chest tomograpy drive the start of antifungal therapy. Finally, while the wise and appropriate employment of all these strategies is very important, recovery from neutropenia is the main prognostic factor. Therefore, every efforts must be devoted to control the underlying disease.

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SP 09

Paroxysmal nocturnal hemoglobinuria pnh

Hanan Hamed

Objective: PNH is a condition in which uncontrolled complement activity leads to systemic complications, principally through intravascular hemolysis and platelet activation. It arises through a somatic mutation of the phosphatidylinositol glycan A (PIG-A) gene in bone marrow stem cells,[1,2] resulting in disruption to glycosylphosphatidylinositol (GPI) biosynthesis.[3]

Results: Among the deficient proteins are the complement regulatory proteinsCD55 andCD59, resulting in increased complement sensitivity of PNH cells, intravascular hemolysis, promotion of inflammatory mediators, and systemic hemoglobin release.[4] Patients with PNH can present with multisystemic clinical manifestations due to intravascular hemolysis, thrombosis and bone marrow failure.[5] Symptoms are therefore often non-specific, ranging from loss of vision (due to retinal thrombosis), headache and nausea/vomiting (due to cerebral thrombosis), pulmonary hypertension (due to pulmonary embolism), anaemia, through to pain and swelling in the lower extremities (due to deep vein thrombosis), renal failure and other symptoms affecting different systems.[6] Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of deaths of which the cause is known. Further, 29% to 44% of patients with PNH have been reported to have at least 1 thromboembolic event during the course of their disease, although the reason(s) a thrombotic event may suddenly occur remains an enigma.[7–9] Platelet activation, complement-mediated hemolysis, impaired nitric oxide (NO) bioavailability, impairment of the fibrinolytic system, and inflammatory mediators are all proposed mechanisms and thought to be responsible for the increased thrombotic risk in patients with PNH. Multiple factors are likely to contribute to any one thrombotic event in patients with PNH.[10]

Conclusion: Therapeutic strategies include terminal complement blockade and bone marrow transplantation. Eculizumab, a monoclonal antibody complement inhibitor, is highly effective and the only licensed therapy for PNH.[11] The therapeutic anti-C5 antibody eculizumab (Soliris, Alexion)

has proven effective in controlling intravascular hemolysis in vivo, leading to remarkable clinical benefit in a majority of PNH patients.[12,13] Yet, persistent C3 activation occurring during eculizumab treatment may lead to progressive deposition of C3 fragments on affected erythrocytes and subsequent C3-mediated extravascular hemolysis, possibly limiting the hematologic benefit of anti-C5 treatment.[14,15] Thus, upstream inhibition of the complement cascade seems an appropriate strategy to improve the results of current complement-targeted treatment.[16,17]

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SP 10

Access to cancer medicines and targeted therapies in developing countries

Zeba Aziz

In LMIC national cancer control programs are barely existent. Emphasis is mainly focused on fighting infectious disease, maternal child mortality and now fighting the Covis-19 catastrophe.

Pakistan is a LMIC with allocation of only 2.7% of the GDP to health. We have approximately 173,937 new cancers and a mortality of 118,442. Health expenditures do not correlate with outcomes especially for the marginalized population. Development and implementation of national NCD control programs for screening of common cancers and early detection are either non-existent or sporadic as a result cancers are usually diagnosed late and present challenges to therapy on all fronts especially in the indigent population.

Challenges include poverty, ignorance, lack of access to cancer centers, lack of access to basic cancer therapy and suboptimal treatment. This includes surgery, radiation and cancer therapy including supportive care. Simultaneously there is a dearth of human resource and cancer care providers to diagnose treat and provide supportive care to cancer patients.

Access to new biologics and targeted therapies present a challenge to the already strained health care budget. Current status of cancer care will be discussed in Pakistan.

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SP 11

Ph-positive and ph-like all: how can we further improve?

Robin Foà

While in childhood ALL the cure rates can be over 80%, in adults the prognosis still remains unsatisfactory. Important advancements have however occurred in the management of adult patients based on the biology of the disease. Ph+ ALL is an illuminating example of how the understanding of a specific genetic abnormality has led over time to the use of targeted therapies. The results obtained with tyrosine kinase inhibitors (TKI) used upfront in adult Ph+ ALL have changed our approach to this condition in patients of all ages. It is thus mandatory that the abnormality is rapidly investigated at presentation. In the GIMEMA network, the presence or absence of the BCR-ABL fusion is tested centrally within one week from diagnosis of ALL, during the steroid pre-phase. TKIs – alone or in combination with chemotherapy – have markedly improved the rates of response and overall survival of Ph+ ALL. The Italian cooperative group GIMEMA over the years has been using an induction strategy based on the use of a TKI (1st, 2nd and 3rd generation) plus steroids and CNS prophylaxis, with no systemic chemotherapy. This has led to a hematologic CR in 94–100% of patients (with no upper age limit) with virtually no deaths in induction. A proportion of patients can obtain a molecular response. Some elderly patients treated only with TKIs are alive and well after many years from diagnosis. Other groups have used a combination between a TKI and de-intensified chemotherapy, in order to reduce the toxicities (and deaths) associated with conventional chemotherapy plus a TKI. With the advent of TKIs, the induction of Ph+ ALL patients – if identified promptly – is a solved issue. Since patients who achieve a molecular response fare significantly better, a molecular response should be the primary endpoint of treatment. Allogeneic stem cell transplant has always been considered the only curative strategy for Ph+ ALL patients. New strategies are however under active investigation. In the last GIMEMA LAL 2116 front-line trial an induction-consolidation strategy based on the use of dasatinib followed by at least two cycles of the bispecific monoclonal antibody blinatumumab were used. This chemo-free induction-consolidation approach is associated with very high rates of molecular response (Chiaretti et al, ASH 2019). In childhood Ph+ ALL, the protocols so far still use an induction based on a combination of chemotherapy plus a TKI.

Great attention has been raised by the so-called Ph-like ALL, a subgroup associated with an unfavorable prognosis. Evidence has been provided that this is contributed by the persistence of minimal residual disease following conventional chemotherapy. Attempts are being carried out by incorporating TKIs or other inhibitors. The GIMEMA LAL 2317 has used blinatumomab in the front-line Ph- ALL protocol (recently

closed) and Ph-like cases are being identified using a predictor described by our group (Chiaretti et al, BJH, 2018). In adult B-lineage ALL, Ph+ and Ph-like ALL account for 35–60% of cases, depending on age, making them the most prevalent genetic ALL subgroup.

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SP 12

CAR T-cell in children all

Francesco Saglio[1,2]

[1] *Pediatric Onco-Hematology, Stem Cell Transplantation and Cellular Therapy Division, Regina Margherita Children's Hospital, Torino, Italy*
[2] *University of Turin, Turin, Italy*

Chimeric Antigen Receptor (CAR)-T cell therapy is emerging as one of the most powerful and promising therapeutictool for the treatment of malignat diseases. CAR-T cells are T-lymphocytes modified *in vitro* to harbor an artificial molecular construct (CAR) made by an extracellular domain consisting of a single-chain variable fragment (scFv) recognizing a specific tumor antigen joined to a transmembrane domain which is linked to the signaling unit CD3ζ and co-stimulatory units CD28 or 4-1BB of the T-cell receptor, making them capable to recognize and to kill tumor's cell in a HLA-independent manner.CAR T-cell therapy consists in the selection of patient's normal T-cells via leukapheresis, activation, transduction to express CARs using lentiviral or retroviral vectors, expansion of transduced cells and infusion of the final product back to the patient. After the CAR T-cells are infused back into the patient, the engineered cells proliferate, recognize and kill tumor cells bearing the specific antigen the CAR is directed against. Most of the current clinical trials have been with anti-CD19 CAR T-cells directed against the antigen CD19, mainly expressed by Acute Lymphoblastic Leukemia and B-cells Non Hodgkin Lymphomas.

In recent years US Food and Drug Administration (FDA) and European Medicine Agency (EMA) approved CD19 CAR T-cells in patients affected by relapsed and refractory ALL under the age of 25 years and this technology is moving from an experimental approach available for very selected patients treated in a small number of Centers to a standard-of-care therapy available almost worldwide.

The diffusion of this technology requires a re-definition of the role of all the other therapy options currently available including other forms of immuno-therapy as monoclonal antibodies, bi-specific monoclonal antibodies and, upon all, allogeneic hematopoietic stem cell transplantation (alloHSCT).

Until now data are limited, and the above-mentioned question is far from being answered but there are some observations derived from pivotal clinical trials that probably will help us in building future trials aimed to define this topic.

Another open question is represented by the persistence of these cells in the patients that is related to the definition of the need for patients responding to CAR-T cells to proceed to other therapies, especially to alloHSCT, to consolidate disease remission. Moreover CAR-T cells are characterized by some peculiar side effects as the Cytokines Release Syndrome or CNS toxicity that if are not properly detected and treated may lead to very severe consequences with a significant mortality rate.

Finally, some technological, practical and economical considerations need to be defined in order to extend the use of this technology worldwide, in respect to the other currently available therapies.

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SP 13

Update on chimeric antigen receptor – T cells (CAR-T) CD19 therapy: the Sheba experience

Arnon Nagler

Chimeric antigen receptor (CAR) T-cell therapy for hematologic malignancies is a cutting edge therapeutic advancement which is leading the immunotherapy frontier and cancer therapy. CD19-specific CARs are the most commonly used. CD19 is expressed on the surface of most B-cell malignancies and thus can be used as a target for immunotherapies for ALL, and NHL. Phase II trials have showed that anti-CD19 CAR T-cell therapy can induce durable responses in patients with relapse/refractory (R/R) ALL and aggressive B cell NHL. Some of the AMLs with 8:21 translocation expressed CD19, as well. We initiated a single center program in which patients with R/R ALL and NHL were treated with academic produced anti-CD19 CAR T-cells (autologous T-cells expressing anti-CD19 CAR construct with CD28 co-stimulatory domain). Inclusion criteria were age between 1 and 50 years, failure of at least two prior therapeutic protocols, a CD3 count greater than 250/μL blood, absence of clinical signs of graft-versus-host disease and no immunosuppressive treatment. Depending on age, the minimal performance score was 50 on a Lansky scale or on a Karnofsky scale. Patients with prior CD19 directed therapies were eligible for the study. Lympho-depleting conditioning was inducted by fludarabine 25 mg/m^2 for 3 days and cyclophosphamide 900 mg/m^2 for 1 day, followed by infusion of 1–1.5 × 10^6 transduced CAR-T cells per kilogram weight. Primary endpoints of the study were production feasibility, patient safety and best overall response rates, documented 1 to 2 months after infusion. 93 patients with r/r B-cell malignancies. All patients were heavily pretreated. Three enrolled patients (3%) dropped out from the study due to clinical deterioration ($n = 2$) or failure to produce CAR-T cells ($n = 1$; absence of CAR-T cells in the infusion product). One patient was treated twice. Of the treated patients, 37 patients had r/r ALL and 53 patient's r/r NHL, including DLBCL ($n = 36$), Burkitt lymphoma ($n = 3$), PMBCL ($n = 7$), follicular lymphoma ($n = 4$), gray zone lymphoma ($n = 1$), mediastinal lymphoma ($n = 1$) and high-grade lymphoma ($n = 1$). The median age of pts with ALL was 17 ± 14 years and median age of those with NHL was 44 ± 15 years. Both, ALL and NHL patients received an average of three prior lines of therapy. Thirty-two of 90 patients (36%) received a stem cell transplantation(SCT) prior CAR-T therapy, including 17 allogenic or haloidentical SCT in patients with ALL ($n = 15$) and NHL ($n = 2$). Ten of 37 (27%) ALL patients received prior

therapy directed against CD19, such as blinatumomab and Inotuzumab. Clinical response was evaluated 1 to 2 months after CAR-T cell administration. One ALL patient died of sepsis before evaluation and one NHL patient is still awaiting his evaluation. Of 36 evaluated ALL patients, 24 (67%) achieved measurable residual disease (MRD) negative CR, 6 (17%) MRD positive CR and 5 patients (14%) progressed. One ALL patient with an initial response was treated a second time with CAR-T, but did not respond. Of 52 evaluated NHL patients, 32 (62%) achieved an objective response, including 16 complete remissions and 16 partial responses. Twenty (38%) patients had disease progression.[1,2] Notably, we recently show that CD19 CAR T-cells were able to induce remission in a patient with CD19+ AML with t (8; 21)(q22;q22.1) that relapsed 6 months post allogeneic transplant and failed re-induction. On day 28 post CAR-T CD19 infusion BM aspiration disclosed normal hematopoiesis with no excess blasts, full donor chimerism and lack of t (8; 21) by FISH confirming clinical and molecular remission.[3] We also assessed kinetic of cell phenotype on PBMCs of the CAR-T treated patients using multiparametric flow cytometry. The manufactured CAR-T products ($n = 9$) were also subjected to immunophenotypic analysis in order to elucidate the mechanisms of CAR-T cell trafficking and activity. We observed increased immunosuppressive phenotype as well as induction of T cell senescence/exhaustion in non-responding compare to responding patients.[4]

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SP 14

Treatment of sickle cell crises

Salam Alkindi

Sickle cell disease (SCD) is an inherited disorder prevalent in Sub-Saharan Africa, Middle East and parts of India. Its characterized by repetitive episodes of vaso-occlusive (VOC) process leading to recurrent painful episodes, hemolytic anemia and predisposition to infection. Sickle cell crises varies and this what brings patients to hospital including VOC leading to recurrent painful episodes, or organ specific complications such as acute chest syndrome, stroke, splenic sequestration, and many skeletal complications. Although the prognosis of patients with SCD has improved, however still these events contributes to decrease quality of life and increased risk of death. Also unfortunately, progress on the management of these acute complications is slow, and tended to be supportive including vaccination, use of antibiotics prophylaxis and blood transfusions. Better understanding of pathophysiology of the disease has allowed more accelerated progress on preventing these complications and development of more focused pharmacological therapies. Hemoglobin polymerization is a primary triggering event in the pathophysiology of the disease, leading to the sickling process, this usually ignite an inflammatory process/tissue ischemia and increased adhesions. This understanding of the pathophysiology has allowed scientist to develop drugs that interfere with these processes such as Voxeletor & Hydroxyurea (interfere with polymerization-both approved by FDA), L-glutamine and Omega 3 (interfere with inflammatory process and oxidative stress) and crizanlizumab and Tinzaparin (works by inhibiting adhesion molecules). This will allow patients and physicians the freedom for a number of therapeutic interventions including development of combinations protocols. SCD is very complex and require a drug with multi-faceted action such as Hydroxyurea and this is of the limiting factors in the new recently approved drugs, limiting the patients who can benefit from each of them. Further progress is also seen in the area of bone marrow transplant (including alternative donor pool) and gene therapy/gene editing.

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SP 15

Secondary acute leukemia evolving from myeloproliferative neoplasm (MPN)

Tariq Mughal

The natural history of myeloproliferative neoplasms (MPNs), both Philadelphia-chromosome positive – [chronic myeloid leukemia(CML)] and negative – [essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF)] has been well documented but the mechanism underlying the apparently inexorable progression from an initial, rather indolent or chronic phase (CP) to advance phase, a term including accelerated phase (AP) and blast crisis (BC) remains obscure. Most patients with MPNs present in the indolent phase, during which myeloid progenitor numbers are greatly increased in the bone marrow and blood. This phase may continue for as little as one year or as long as 20 years or more, but eventually it transforms into acute leukaemia (BC), in which an increasing proportion of blast cells are found in the marrow and peripheral blood. The risk associated with the development of advanced-phase disease differs depending on the MPN subtype and is influenced by a number of factors such as duration of disease, clinical factors, the presence of

unique molecular genetic features, and in some cases, the therapeutic interventions. ET probably carries the lowest rate of transformation to acute myeloid leukaemia (AML), whereas MF may carry a relatively high risk; lymphoid transformation has been reported in rare cases. The risk of transformation in CML to BC in the *ABL1*-tyrosine kinase inhibitors (TKI) era appears to be quite low, <2% per annum. Transformed disease in general tends to be difficult to be managed and is associated with a poor prognosis. The best treatment strategy, therefore, remains the prevention of transformation. Allogeneic stem cell transplantation is currently the only treatment that has been observed to confer long-term benefit to a small minority of patients who qualify for it. In this presentation, I will address the evolving genetic landscape, translational research efforts and investigational therapies for transformed MPNs.

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SP 16

The new European leukemianet recommendations for treating CML

Rüdiger Hehlmann

Twenty-two years after the first patients with chronic myeloid leukemia (CML) were treated with the tyrosine kinase inhibitor (TKI) imatinib, outcome exceeds all expectations: the vast majority of CML patients have achieved normal life expectancy and some patients in sustained deep molecular remissions (DMR) may even be operationally cured in durable treatment-free remissions (TFR). However, some expectations remain unmet. Most patients are not yet cured and require life-long maintenance therapy. Also, progression to blast crisis still occurs in 5–7% of patients and remains a challenge. CML has not become the expected model disease for treating other leukemias or cancers, but the principle of elucidating the pathogenesis as a successful approach for cancer treatment has been impressively demonstrated in CML.

New insights have emerged from maturing long-term academic and commercial clinical trials regarding optimum management of CML. Velocity of response has unexpectedly proved less important than hitherto thought, does not predict survival, and is of unclear relevance for TFR. Serious and cumulative toxicity has been observed with TKI that had been expected to replace imatinib. Generic imatinib has become cost-effective first-line treatment in chronic phase despite chronic low-grade side-effects in many patients. Earlier recognition of CML end-phase by genetic assessment might improve prospects for blast crisis. Treatment discontinuation and TFR has become an important new treatment goal of CML. Duration of DMR (MR4, MR4.5) may be the best predictor of success. To reflect this new situation, the European LeukemiaNet has recently revised and updated its recommendations for treating CML. The presentation will focus on recent developments and on current evidence for treating CML in 2020.

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SP 17

Ex vivo activation of pleural T cells in pleural malignancies

Vera S. Donnenberg, James D. Luketich, Albert D. Donnenberg

Introduction: MPE are uniformly fatal. It is estimated that the incidence of MPE in the United States is more than 150,000 cases per year, making this a common terminal pathway for a variety of cancers and a dire problem without a solution. Currently available cellular therapeutics are costly and often lack polyclonality, polyfunctionality, and the ability to persist as central memory. The treatment of this deadly complication is potentially at a turning point if the rich immune infiltrates that characterize the majority of effusions can be redirected to an efficacious anti-tumor response. Despite this promise, pleural immune infiltrates have not been used to generate effector cells for adoptive cellular therapy.

Objectives: We have exploited the heterogeneous cellular composition of MPE by piloting the generation of therapeutic T-cell products, using conventional methods used for expanding tumor-infiltrating lymphocytes (TIL). The advantages of plural T cells are: (1) Fewer cycles of expansion owing to several orders of magnitude greater starting number of T cells; (2) Greater initial clonal and functional heterogeneity; (3) Likelihood of preserving polyclonality, polyfunctionality and central memory.

Results: MPE have abundant tumor infiltrating CD3+ T-cells, CD19+ B-cells, CD14+ macrophages, and EpCAM-/Cytokeratin+ mesothelial cells. Regulatory T-cells, which may be abundant in TIL, are low or absent in MPE. Our laboratory's average recovery of viable nucleated cells per MPE is $7.8 \pm 4.0 \times 10^8$ cells, with viability exceeding 95%. The cellular composition (tumor, lymphocytes, macrophages, neutrophils, mesothelial cells) varies from patient to patient, but T-cell recovery averages $2.0 \pm 1.6 \times 10^8$ (mean, SD). In pilot experiments we cultured whole breast cancer MPE in the presence of anti-CD3/anti-CD28 Dynal beads, IL-2 and IL-7 for 96 h. CD3+ T cells were FACS-sorted and added to autologous tumor monolayer cultures and expanded for an additional passage (2 weeks). Expanded passage 2 T cells were compared to freshly isolated T cells (2nd MPE drainage) for ability to kill autologous tumor and non-tumor targets (live cell imaging). Expanded T cells were potently cytotoxic, whereas freshly isolated MPE had no activity against autologous tumor. Expanded T cells did not kill the autologous non-tumor target (adherent cells isolated from peripheral blood). Additionally, we tested freshly isolated breast cancer MPE T cells for the ability to secrete cytokines associated with expansion and effector generation (IL-2, IFNγ and TNFα). We also measured the immunosuppressive cytokine IL-10. Freshly isolated plastic nonadherent cells from a breast cancer MPE were incubated with TPA+ ionomycin for 1 h, followed by brefeldin for 2 h. CD4+ T cells (85%) and CD8+ T cells (9%) were gated on cells co-expressing intracellular IL-2 and IFNγ. Polyfunctional T cells, defined as IL-2+/IFNγ+/TNFα+/IL-10-, comprised 0.38%, and 0.82% of CD4+ and CD8+ T cells. Unstimulated control cultures constitutively secreted IL-10 and IFNγ but not IL-2 or TNFα.

Conclusions: Pleural infiltrating T-cells represent an attractive source of T cells for immunotherapy. They are numerous, readily expandable without protracted passage and can be induced to secrete immunostimulatory and effector cytokines and specifically kill autologous tumor.

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SP 18

Are there really cancer stem cells and how do they operate?

Robert Gale

Some but not all data suggest within a cancer not all cancer cells are the same, namely, there are diverse cell types. The *stem cell* theory of cancer proposes amongst all cancer cells a very few act as *stem cells*. These cells reproduce themselves and sustain the cancer much like normal stem cells renew and replenish organs and tissues like the haematopoietic system. There are important therapy implications if cancers are really driven by a few *stem cells*. For instance, many anti-cancer therapies are evaluated based on their ability to make a cancer smaller. This can happen without killing cancer *stem cells*. If so, the cancer is likely to recur, perhaps in a more dangerous form such as metastases. In fact, most people with cancer die from metastases, not the primary cancer. The analogy is selecting a more virulent microbe by indiscriminate use of antibiotics.

One component of the cancer *stem cell* theory concerns how cancers arise. Typically, for a cell to become cancerous it must accumulate substantial numbers of mutations. A leukaemia such as chronic myeloid leukaemia (CML) is an exception caused by 1 mutation (*BCRABL1*). Conventional cancer theory is that any cell has the potential to become a cancer. However, other data suggest only some cells, those with *stem cell* potential, can develop into a cancer. This may explain why some normal people can have cancer-related mutations without having cancer, for example normals with *BCRABL1* or normals with t(14;18) without CML or without a lymphoma. The hypothesis is the cell(s) in which these mutations occur are not *stem cells* and therefore lack the potential to cause cancer. However, we must also consider the possibility some mutations can re-programme a cell without *stem cell* potentially to become a *stem cell*. An example of this are induced pluripotent stem cells iPSC) which are adult (non-stem) cells reverted to an *embryonic stem cell* state by introducing 4 genes. Another notion is only cells with *stem cell* like features survive sufficiently long to accumulate the typically large number of mutations required for cancer development. The theory, therefore, is cancer *stem cells* arise from normal *stem cells* or *precursor cells* produced by normal *stem cells*.

Another important implication of the cancer *stem cell* theory is cancer *stem cells* are closely related to normal *stem cells* and share many properties. Cancer cells produced by cancer *stem cells* should follow many of the rules observed by normal daughter cells. In this regard cancer cells can be considered a caricature of normal cells with similar but distorted features. If so, it may be possible to use knowledge about normal *stem cells* to identify and attack cancer *stem cells*.

Lastly, it may not be necessary to eradicate all cancer stem cells to cure a cancer. For example, in CML, therapy with tyrosine kinase-inhibitors (TKIs) markedly reduces numbers of mature leukaemia cells but not any and certainly not all CML *stem cells*. Regardless, in a substantial proportion of people with CML responding favorably to TKI-therapy it is possible to stop therapy without leukaemia returning. In sum, increasing knowledge of cancer stem cells should improve our understanding of and ability to treat diverse cancers.

Prof. Robert Peter Gale, Haematology Research Centre, Department of Immunology and Inflammation, Imperial College London, London, SW7 2AZ UK T:001-908-656-0484; E:robertpetergale@alumni.ucla.edu.

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SP 19

Challenges in treating solid tumors in developing countries

Adnan Abdul Jabbar

There is an increasing number of cancers worldwide due to epidemiological transition. Longer life spans resulting in aging population is among some of the reasons for growing burden in cancer worldwide. The number of new cancer cases is expected to increase by nearly 75% by 2030 (107,000 additional cases per annum), with 60% of cases in the elderly (aged ≥65). The extent of cancer related morbidity and mortality is directly linked to the effectiveness of efforts to prevent, control and treat cancer, particularly in the developing world. In 2012, almost 57% of all cancer cases and 65% of cancer deaths occurred in low-and middle-income countries. If the current trend continues, the burden of cancer will increase to 22 million new cases annually by 2030, with 81% of new cases and almost 88% of mortality occurring in less developed countries. Cancer care in a country like Pakistan is challenging because of lack of strategic information and national planning for cancer control. Cancer registry provides important information that helps in directing and planning cancer prevention and care. Lack of national cancer registry limits estimation of true burden, identification of areas that require special need and thereby proper treatment strategy. Health systems required to deliver comprehensive life-saving treatments are limited in the country. Out of pocket payments and private health care usage remains high. A number of patients are not covered by insurance and individuals face catastrophic expenditure in seeking treatment. As a result, there is disparity in access to quality care. High incidence of later stage disease is very common due to social stigma associated with cancer treatment, myths, lack of awareness and preference for alternative treatment options. Drugs that have lately revolutionized cancer management are either not available in the country and if present, are extremely expensive for a common person to afford. Palliative care and access to supportive care medicines is almost nonexistent. Pain management is restricted to analgesics without narcotics. With cancer rates steadily rising in low- and middle-income countries, the disease will inevitably

frustrate global development efforts unless urgent action is taken.

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SP 20

Lymphoblastyc lymphoma/leukemia: a single center experience

Alina Antipova, Olga Baranova

Introduction: Lymphoblastic lymphoma (LBL) is a rare neoplasm of lymphoblasts or precursor T- and B-cell with predominantly involves lymph nodes, mediastinum or extranodal tissues with minimal persistence in bone marrow. LBL amount 2% of all non-Hodgkin lymphomas. T-phenotype is the most common one and reaches above 80% of LBL. LBL and acute lymphoblastic leukemia (ALL) have the same biological entity according WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues 2017. Distinguishing criterion between two diseases is the number of bone marrow blasts 25%. ALL-regimen provide better overall (OS) and disease-free survival (DFS) in contrast with CHOP-like schemes.

Patients and methods. A retrospective review of LBL patients from **N.N. Blokhin National Medical Research Center of Oncology** (Russia, Moscow) during period between 2009 and 2020 was done. Patients were treated according ALL-2009 protocol (Russian ALL-Study Group, ClinicalTrials.gov NCT01193933). Kaplan–Meier curves and log-rank test were used to evaluate the OS and DFS. This study includes 20pts with primary ($n=15$) and relapse LBL ($n=5$). T-cell LBL pts were 18, and 2 were of B-cell lineage. Most patients were males 85% (17 of 20). Stage II and IV both at 45%, stage III 10%. All T-LBL patients showed a mediastinal tumor, B-LBL pts had involved peripheral lymph nodes and soft tissues. The rate of LBL among all primary lymphoid precursor neoplasms (LBL and ALL) was 17.6%. Median follow up was 28 months (0.5–170.5 mo).

Results: All 5 relapse patients were pre-treated out of our center: after CHOP-like treatment with relapse in initial zones and all died from disease ($n=3$), after HyperCVAD, later followed alloHSCT ($n=1$, alive) and 1 pts after ALL-BFM-2002 with mediastinum and CNS relapse. CR rate of primary LBL ($n=15$) was 93%, 1 pts was refractory and later died. Radiotherapy has been carried out in 40% (6 of 15) patients with residual tumor mass after chemotherapy consolidation. 1 patient was been undergoing autoSCT. The 10-year OS of patients with LBL, T-ALL and B-ALL was 73.8%, 48.7% and 54.5% respectively ($p=0.3$). The 10-year DFS in the same groups was 75%, 56.3% and 64.5% respectively ($p=0.2$). Although the results are not statistically significant, we see a trend towards better survival outcomes in patients with LBL. AlloSCT was performed in 2 patients LBL in CR2, one of them alive, the other died of complications.

Conclusion: The results of treatment of LBL pts in **N.N. Blokhin National Medical Research Center of Oncology** are comparable to most of the similar reported studies. The survival results of LBL patients with ALL-regimen therapy seem to be better compared with patients ALL. CHOP-like chemotherapy is a very poor prognostic factor for LBL patients. The role of autoSCT has not been developed. In our center we have satisfied outcomes of LBL with minimal rate of high dose consolidation with autoSCT. Radiotherapy at postconsolidation phase in patients with residual tumor mass reduces the risk of relapse.

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SP 21

Relapsed and refractory classical Hodgkin lymphoma immunotherapy

Kirill Lepik

Liudmila Fedorova, Elena Kondakova, Yury Zalyalov, Andrey Kozlov, Marina Popova, Anastasia Beynarovich, Nikita Volkov, Polina Kotselyabina, Artem Gusak, Vadim Baykov, Alexandr Kulagin, Natalya Mikhailova

Background: Introduction of PD-1 inhibitor nivolumab (Nivo) into a clinical practice revolutionized the treatment of relapsed and refractory classical Hodgkin lymphoma (r/r cHL). Yet there is a set of unresolved clinical questions including the assessment of response, the prognostic factors influencing the survival of patients during immunotherapy, and optimal treatment strategy in patients resistant to nivolumab, as well as the possibility of discontinuation of therapy in case of persistent complete remission. This report presents the results of analysis of nivolumab treatment outcomes in Pavlov University.

Methods: This retrospective study included r/r cHL patients treated with standard-dose nivolumab (3 mg/kg q2w). Therapy was continued until the disease progression, signs of intolerance or could be stopped at the discretion of treating physicians in selected patients with prolonged complete remission. In patients with r/r disease after nivolumab monotherapy, 48 received nivo and bendamustine (Benda) in a 28-day cycle. Benda (90 mg/m^2) was infused on day 1,2 and Nivo – on day 1 of the cycle. The response was assessed by PET-CT scan every 3 months according to LYRIC criteria.

Results: The analysis included 116 patients treated with nivolumab monotherapy (56 m/60 f) with a median age of 32 years (range 14–63). With a median follow-up of 41 (6–54) months after treatment initiation, 108 (93%) patients were alive, the median OS was not reached. Median PFS was 19 mo (13.7–24.4) with a 3-year PFS of 27%. The best overall response was CR in 33%, PR in 34%, SD in 5%, PD in 9%, an indeterminate response (IR) in 20% of pts. Patients with early CR at 3mo after treatment initiation had significantly better prognosis (median PFS 35 mo vs. 17 mo, $p=0.008$). Other clinical factors that predicted prognosis were B-symptoms (median PFS 15 mo vs. 26 mo, $p=0.017$), extranodal disease at the moment of the treatment initiation (median PFS 14 mo vs. NR, $p=0.000$), >4 prior lines of therapy (median PFS 18mo vs. 27 mo, $p=0.05$). In a group of patients ($n=23$) who discontinued nivolumab in complete response (CR), the possibility of durable remission achievement was demonstrated (2-year PFS was 55.1%). The nivolumab retreatment has demonstrated the efficacy with high overall response rate (ORR) and CR (67 and 33.3% respectively). In the group of patients receiving nivo-benda combination after nivolumab monotherapy failure, the

median follow-up was 29 (4–38) months, with the median PFS of 9.8 mo (7.4–12.2). The median OS was not reached, 89.6% of patients were alive. The overall response rate (ORR) was 75% including complete remission (CR) in 44% pts. The progressive disease (PD) was the best response in 10% of pts. The allo-HSCT after Nivo was performed in 14 (29%) pts.

Conclusion: Nivolumab is highly efficient in the treatment of r/r cHL with early complete response, B-symptoms and extranodal disease at the treatment initiation being the most significant prognostic factor of PFS duration in our population of patients. The therapy may be discontinued in selected patients with complete remission. Combination of nivo with bendamustine is effective and safe approach for patients with r/r cHL after nivo monotherapy failure.

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SP 22

Literature review: the year in apheresis – what is new?

Joseph Schwartz

Since 1986, the American Society for Apheresis (ASFA) has published practice guidelines on the use of therapeutic apheresis in the Journal of Clinical Apheresis. Since 2007, the guidelines are published in regular intervals to reflect current evidence-based apheresis practice with the most recent edition published in 2019. The ASFA guidelines are written in a user-friendly fact sheet format and represent a concise yet comprehensive review of the English language literature on the use of apheresis to treat disease. The role of the guidelines is to provide the most current information available to apheresis practitioners. The PEXIVAS study is an international, randomized controlled trial comparing therapeutic plasma exchange (TPE) versus no TPE and steroid dosing regimen on the primary composite outcome of end stage renal disease or death in patients with ANCA-associated vasculitis. The study was published in early 2020 in the NEJM. This is the largest study on the role of therapeutic apheresis in ANCA-associated vasculitis published to date. The study showed the TPE does not reduce the risk of ESRD or death in patients with ANCA-associated vasculitis. Based on these findings, an interim updated fact sheet was recently published. In this interim fact sheet, the category recommendation for rapidly progressive glomerulonephritis in the setting of microscopic polyangiitis, granulomatosis with polyangiitis, or renal-limited vasculitis with Cr $\geq$5.7 mg/dL (includes "on dialysis") was changed from category I to category II. Similarly, the grade of evidence was changed from IA to IB to acknowledge previously described important limitations of the PEXIVAS study including the lack of biopsy to define disease severity and the long follow-up period, which may make it difficult to detect initial improvement in the subset of patients at first presentation. This recent seminal publication and its implication for therapeutic apheresis will be discussed. Other topics with new information that will be addressed in this presentation include Hereditary TTP. A recent review on the prevalence, pathogenesis, clinical features of this disorder, as well as therapeutic options was published. Although Hereditary TTP is not currently categorized in the Therapeutic Apheresis guidelines, indications for TPE as well as the use of plasma infusion, and eventually rhADAMTS13 enzyme in this disorder will be discussed. Similarly, Hemophagocytic Lymphohistiocytosis/Macrophage Activating Syndrome (HLH/MAS) will be reviewed including a recent retrospective case series showing use of TPE in combination with immunosuppressive therapy in this disorder.

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SP 23

The ASFA therapeutic apheresis guidelines – 8th edition – overview with focus on hematology/oncology indications

Nancy M. Dunbar

The ASFA Journal of Clinical Apheresis (JCA) Special Issue Writing Committee is charged with reviewing, updating, and categorizing indications for the evidence-based use of therapeutic apheresis every 3 years to produce "Guidelines on the Use of Therapeutic Apheresis in Clinical Practice: Evidence-Based Approach" which is published in the Journal of Clinical Apheresis. Guideline preparation incorporates systematic review published peer reviewed literature and applies evidence-based approaches in the grading and categorization of apheresis indications. These guidelines serve as a key resource to guide the utilization of therapeutic apheresis in the treatment of human disease. In this session, we will review the evolution of the guidelines and highlight significant changes in the 2019 Journal of Clinical Apheresis 8th Special Issue published in June 2019. Recommendations for the use of therapeutic apheresis for Hematology/Oncology Indications will be briefly reviewed.

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SP 24

Essential molecular characterization of AML patients

Mehmet Yilmaz

Several recurrent somatic mutations have been identified as important features in defining the molecular landscape of AML. Targeting mutations such as FLT3 remained an area with active investigations and variable success while targeting other common mutations such as NPM1, DNMT3A, and TET2 remains challenging.

Cytogenetic characterization of AML: These abnormalities include: AML with t(8;21)(q22;q22); RUNX1-RUNX1T1, AML with inv (16)(p13.1q22) or t (1 6; 1 6) (p 1 3. 1; q 2 2); CBFB-MYH11, AML with t(15;17)(q22;q12); PML-RARA, AML with t(9;11)(p22;q23);MLLT3-MLL, AML with t(6;9)(p23;q34); DEK-NUP214, AML with inv (3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1, AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL14, A recent revision of WHO classification in 2016 has recognized new provisional category of AML with BCR-ABL1. Patients with BCR-ABL1 AML are less likely to have splenomegaly or peripheral basophilia and usu-

ally have lower bone marrow cellularity and myeloid/erythroid ratios compared to CML-BC.

Mutations in signaling pathways: Mutations in FLT3 receptor can lead to constitutive activation that in turn can lead to decrease in apoptosis and increase in leukemia proliferation and survival. Patients with FLT3/ITD mutations typically have high white cell counts at disease presentation and have normal or intermediate risk karyotypes. FLT3/TKD mutations tend to confer slightly better prognosis. NPM1 mutations usually occur in exon 12 in the C-terminus of the protein and can lead to cytoplasmic localization of NPM1 protein. Studies have shown that NPM1 mutations usually carry a favorable prognosis in the absence of FLT3-ITD and mainly in the presence of IDH1-2.

Other gene mutations in AML: ASXL1 gene encodes a chromatin binding protein, which in turn enhance or repress gene transcription in localized areas by chromatin structure modification. The overall frequency of ASXL1 mutations in AML is approximately 3–5% but its incidence is higher in patients with intermediate risk AML. DNMT3A is a DNA methyltransferase that regulates epigenetic alterations through DNA methylation. DNMT3A mutations are frequently found with FLT3-ITD, NPM1, IDH1-2 mutations though rarely associated with t (15; 17) and CBF leukemia's. IDH1 and IDH2 are two enzymes that play an important role in DNA methylation and histone modification and affect the active isocitrate binding site and lead to increased level of 2-hydroxyglutarate. IDH2 mutations occur in 8–12% of adult AML. 2-HG can be detected in vast excess in the serum and BM of AML patients with IDH1/2 mutations, suggesting that it may serve as a biomarker for this genetically defined subset of AML patients and as a measure of residual disease after AML therapy.

Mutations in cohesion complex members; BCOR, PHF6;

Mutations in splicing machinery: The most common splicing factor gene abnormalities involved in AML are SF3B1, U2AF1, SRSF2, and ZRSR2. These mutations are mutually exclusive and can be defined as founder mutations or associated with certain phenotype in a subset of patients such as SF3B1 mutations in MDS patients with ring sideroblasts and SRSF2 in chronic CMML.

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SP 25

How clinical networking may be a powerful strategy to face the challenges faced by hematologists treating acute leukemias in the developing world. The experience of the International Consortium on Acute Leukemia (ICAL)

Eduardo M. Rego

The International Consortium on Acute Promyelocytic Leukemia (IC-APL), later renamed as International Consortium on Acute Leukemias (ICAL), was founded in 2004 as an initiative of the International Members Committee of the American Society of Hematology (ASH). Its goal was to create a network of institutions in developing countries that would exchange experience and data and receive support from well-established cooperative groups, bringing together clinical investigators from Europe, North America and Latin America. The Consortium selected acute promyelocytic leukaemia (APL) as a model disease to test the impact of networking on the outcome of patients treated in developing countries, because it is a highly curable disease, if early diagnosis and specific treatment are promptly established. By the end of the 1990's, European and American groups reported complete remission (CR) and long-term disease-free survival (DFS) rates of approximately 90% and 85%, respectively, in studies of cohorts of APL patients who were treated with all trans retinoic acid (ATRA) and anthracyclines (Soignet et al., 1997; Sanz et al., 1999). In contrast, a retrospective analysis of 134 Brazilians patients with APL treated between 2003 and 2006 reported a death rate of 32% during induction, with most of the deaths caused by APL-associated coagulopathy (Jacomo et al., 2007). In this study the long-term overall survival (OS) rate at 2 years was less than 60%, indicating a clearly unmet medical need. The consortium adopted the combination of ATRA and anthracycline, using the same design of the PETHEMA/HOVON LPA2005 protocol (Sanz et al., 2010, 2015), except that idarubicin was replaced by daunorubicin at a ratio of 1:5. Importantly, medical educational activities, centralized laboratory diagnosis and monitoring and specific guidelines for supportive treatment were adopted. Here we will present the analysis of 306 Brazilian patients treated according to the IC-APL protocol and discuss the achievements and pitfalls that the group has faced during its 16-year experience. In total Number of screened patients: 374 patients were screened and 306 were considered elegible with an average of 25.4 pts/year. The main reasons of ineligibility were PML/RARA was not detected (36%); previous chemo or radiotherapy (12%), drug unavailability (10%); age >75 y (8%); pregnancy (7%). One case of ZBTB16/RARA rearrangement was detected. The median time of follow up was of 50 months. The Complete Hematological Remission was of 88.9% and the number of deaths during induction among eligible patients was of 33 (10.7%). The Cummulative Incidence of Relapse was 13% (35/265 pts) and most relapses occurred during maintenance relapse (21 pts). Monitoring was successfully performed by RT-qPCR and conventional RT-PCR. With discrepant results in only 7 patients (in whom relapse was first detected by RT-qPCR). The 10-year overall survival rate was of 75% (95% CI: 68–80%) and the 10-year disease free survival was of 82% (95% CI: 75–87). The ICAL experience confirmed that the establishment of clinical networks involving developing and developed countries may be a powerful strategy to face the challenges faced by hematologists treating acute leukemias in the developing world.

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SP 26

Novel approaches to the treatment of polycythemia vera

Martin H. Ellis

Since the times of Vaquez and Osler over one hundred years ago phlebotomy has been has been a mainstay of treatment in Polycythemia vera (PV) and for more than fifty years, cytore-

ductive agents have been added to achieve hematocrit control in patients at high risk for thrombosis. Thus PV has lagged behind other hematologic malignancies in the implementation of novel and targeted drug therapy. This has changed recently with the development of novel therapies for this disease, a number of which have received regulatory approval internationally.

Ruxolitinib has been approved as second line therapy for PV patients intolerant of or resistant to hydroxyurea on the basis of the RESPONSE trial. In this study 222 patients were randomized to receive ruxolitinib or best available therapy (BAT) in the second line setting. At 5 years 60% of the ruxolitinib patients versus 19% of the BAT patients maintained hematocrit control without need for phlebotomy. Reduction in spleen volume was also more frequent among ruxolitinib patients (89 vs. 49%). There were decreases in *JAK2* V617F allele burden in both groups but complete molecular remissions were rare. Importantly, herpes zoster infections occurred among ruxolitinib treated patients.

Interferon has become an important drug in the treatment of PV with the publication of interim and final results of a number of studies of pegylated versions of interferon. The Myeloproliferative Disorders Research Consortium (MPD-RC) 112 and MPD-RC 111 randomized studies previously treated and untreated patients respectively. Good clinical responses with manageable toxicity were attained and further follow up is awaited. The 3 year results of the combined PROUD-PV and CONTINUATION-PV, randomized, phase 3 trials comparing ropeginterferon (a novel, long-acting, mono-pegylated proline interferon) to hydroxyurea in newly diagnosed PV patients show improved complete haematological response and reduced *JAK2* V617F allele burden with ropeginterferon. The drug is also under study in patients with low-risk PV in whom hematocrit levels at or below 45% compared with those who received monthly phlebotomy alone were more common according to interim findings from the ongoing LOW-PV trial.

Novel agents for PV include MDM2 inhibitors, nutlins. MDM2, an inhibitor of *TP53* is up-regulated in PV CD34+ cells and exposure to a nutlin induced *TP53* and selective stem cell depletion in preclinical models. Early trials of idasanutlin, an oral MDM2 antagonist demonstrated a 58% overall response rate and median duration of response of 16.8 months in high-risk PV patients after failing prior therapy. Idasanutlin is being evaluated in a multinational phase 2 trial.

A unique approach to controlling the hematocrit in PV by targeting iron metabolism is currently in early testing. Hepcidin is the major physiologic regulator of iron metabolism. PTG-300 is a first-in-class synthetic hepcidin mimetic that is in phase 2 clinical trial development. The agent reduces iron available for erythropoiesis and in a preliminary study was able to maintain the hematocrit at <45% without need for phlebotomy in a small number of PV patients all of whom were previously phlebotomy dependent.

These novel agents and others will likely change treatment paradigms in PV.

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SP 27

New drugs for low grade lymphoproliferative diseases

Argiris Symeonidis

For asymptomatic patients with low-grade lymphoproliferative disorders and low tumor burden, watchful waiting represents a rational approach. For symptomatic patients or for those with high tumor burden, initial treatment is usually chemoimmunotherapy with an anti-CD20 monoclonal antibody (mo-Ab), most commonly Rituximab or Obinutuzumab plus an alkylator, such as bendamustine or chlorambucil and/or a pourine analog, such as fludarabine or cladribine. For the Refractory/Relapsed (RR) setting treatment options depend on patient's background, initial PFS and on various prognostic parameters. Newer anti-CD20 mo-Abs, such as Ublituximab appear equally effective, but have not yet been tested comparatively with the previous ones. Radioconjugates such as 90Y-ibritumomab tiuxetan and 131I-tositumomab are no more in broad use due to unpredicted myelotoxicity. The newer 90Y-epratuzumab tetratexan appears safe as consolidation following R-CHOP in DLBCL patients. Polatuzumab vedotin, Pinatuzumab vedotin and Tafasitamab targeting CD19 have mainly been used, combined with an anti-CD20 mo-Ab to treat RR-DLBCL with success, which render them candidates for indolent lymphomas also. BTK inhibitors represent one main treatment option, either as initial treatment or in the RR setting. Ibrutinib, the first in class drug, is used either alone or in combination with Mo-abs and/or alkylators. Acalabrutinib, already approved for CLL/SLL and MCL, is now being tested for other B-cell malignancies. Zanubrutinib, a newer analog not exhibiting some of ibrutinib's AE, has been approved for RR-MCL and is currently being evaluated alone or in combination with Mo-Abs, lenalidomide and other agents. Idelalisib, the first PI3K-inhibitor, the second family of highly used targeted agents, has been approved for CLL/SLL and FL. Duvelisib, Copanlisib and Umbralisib are newer agents coming up and are currently being tested usually in combination with mo-Abs or other agents. Bimiralisib, a dual PI3K/mTOR inhibitor is a promising agent still in phase I. Hepatotoxicity, the major AE of this class, is reversible and dose-dependent. The BCL2 inhibitor venetoclax, alone or combined with mo-Abs and/or bendamustine (BRVen) or with Ibrutinib (ongoing trial), is a breakthrough approach, being tested in several disease entities with impressive results. Bispecific antibodies engaging CD19 (Blinatumomab) or CD22 (Inotuzumab ozogamycin) to a T/NK-cell surface antigen have received approval for more aggressive B-cell lymphomas. Lenalidomide combined with Rituximab (R2) has demonstrated impressive results as initial treatment in FL and the newer cereblon-modifier Avadomide is now being tested in combination with Obinutuzumab in RR B-cell lymphomas of all types. Lenalidomide with Blinatumomab is also tested in an ongoing study. mTOR/NF-κB inhibitors (temsirolimus, everolimus) are not so effective as single agents but can be combined with various targeted and/or cytotoxic agents and construct synergistic regimens. Tazemetostat a novel EZH2 inhibitor recently received accelerated approval by FDA for patients with RR-FL and EZH2 gene mutations, following the

results of a phase-II study. Combinations of this drug with other agents are also expected. Immune check point inhibitors (Nivolumab, Pemprolizumab, Atezolizumab) are promising as third line treatment and beyond. Other agents under investigation include the inhibitor of nuclear export selinexor, the SYK inhibitor entospletinib, the dual SYK/JAK inhibitor certulatinib and the CDK inhibitors flavopiridol and dinaciclib.

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SP 28

Which aggressive B cell lymphoma should not be treated with RCHOP?

Christian Gisselbrecht

The standard treatment of high-grade B cell lymphoma with RCHOP did not change yet despite the description of the biological heterogeneity. With an overall survival rate superior to 80%, patients with an IPI score 0–2 define a good prognosis group and there is no need to modify this approach if chemotherapy still remain the main tool. How can you characterize high risk aggressive B cell Lymphoma? Important progress has been made in our understanding of the biology and immunology of the group of diseases now included within DLBCL, and now there is an expanding list of active, targeted options. The integration of molecular, genetic, and metabolic imaging studies is essential for clinical trials involving the rational assembly of drugs with various mechanisms of action and immunologic properties. Several adverse factors have been described, closely related to the technology used. In a first historical approach DLBCL can be biologically isolated in GCB and non-GCB subtype with a different outcome, Double hit Myc, Bcl2 translocations, or double expressors Myc, Bcl2 are associated with a poor prognosis. Attempts have been made to elaborate a new classification that integrate next-generation sequencing. In this heterogenous high risk lymphoma, RCHOP needs to be improved. Several targeted agents have been added to RCHOP however none of these new regimens were able until now to improve the outcome in randomized study. Another approach is to detect earlier patients still not achieving a satisfactory response. The percentage of is close to 30% and reflects the heterogeneity of the disease. Detecting early failure of response can be done by incorporating an evaluation with PET scan at diagnosis with the metabolic tumour volume and after two or four cycles for the quality of response. What can we propose for this population? Salvage chemotherapy and stem cell transplantation is the most common practice. Several studies have showed an improvement of survival for the patients with pet positive after two cycles. However, half of the patients will not be eligible for transplantation due to ineffective salvage treatment, and the other half will relapse after ASCT. There is clearly a need for new drugs that improve salvage efficacy. Impressive results have been reported with CAR-T cell engineering with a high response rate in refractory patients lasting over two years at the last report. This new approach will revolutionize the treatment of lymphoma.

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SP 29

How can we estimate early relapsed follicular lymphoma and how can we treat?

Ozan Salim

FL is the most common indolent non-Hodgkin lymphoma, generally with favorable outcomes (median overall survival [OS] >20 years). The median age at diagnosis is 65 years. Treatment options, both in the front line and in the relapse setting, are observation, immunotherapy and chemo-immunotherapy. The addition of rituximab to standard chemotherapy has significantly improved the OS. However, current treatment options for FL is not curative and a subgroup of the patients has a more aggressive clinical course (early progression, histologic transformation). Histological transformation of FL occurs at a risk of 2% per year. At the time of diagnosis, the FL international prognostic index (FLIPI) and tumor grade are used to distinguish low-risk from high-risk patients. Median progression free survival (PFS) by the FLIPI risk group was 84, 70, and 42 months for low, intermediate, and poor risk disease, respectively. POD24-PI and m7-FLIPI scores are also investigated to predict progression free survival (PFS) in a large cohort of patients receiving first-line chemo-immunotherapy. At the time of relapse, the best available predictor of poor survival is the duration of remission following initial treatment. Relapse of FL within 24 months of chemo-immunotherapy (POD24) occurs in approximately 20% of patients. POD24 was significantly associated with inferior OS at 5 years (50% vs. 90%). The FLIPI, m7-FLIPI, and POD24-PI have been evaluated to identify POD24 patients. Sensitivity and specificity of these prognostic indices in POD24 are 70–78% and 56–58% for high risk FLIPI, 43–61% and 79–86% for high risk m7-FLIPI, 61–78% and 67–73% for high risk POD24-PI, respectively. Furthermore, gene expression profiling and circulating tumor/cell-free DNA are other emerging methods for predicting POD24. However, there is no standardized method to prospectively predict POD24. Patients with relapse FL should undergo an excisional biopsy before initiating next therapy to confirm relapse and exclude histologic transformation. Because no treatment modality has been shown to be superior to another in this situation, POD24 patients should be encouraged to participate in clinical trials whenever possible. If a patient is not a candidate for a clinical trial, treatment options include chemo-immunotherapy (such as bendamustine plus obinutuzumab(O) or O-CHOP) and targeted therapies (such as immunomodulators and PI3K inhibitors). For fit patients age <65 years without an appropriate clinical trial option consolidative autologous stem cell transplant should be considered to induce prolonged remissions and improve prognosis. Nevertheless, there is an unmet need for better identification and treatment of POD 24 patients.

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SP 30

Exosomes in heme malignancies and pre-cancerous states

Rajko Kusec

Department of Hematology, Division of Molecular Diagnostics and Genetics, University Hospital Dubrava and School of Medicine University of Zagreb, Zagreb, Croatia

Diverse physiologic and pathologic processes, such as angiogenesis, immune cell phenotype, cell differentiation and fate, epithelial to mesenchymal transition and apoptosis are maintained by extracellular vesicles (EV), small membrane vesicles released from most cell types into the extracellular space as vehicles of intercellular communication. EV subtype are exosomes, 30–100 nm in diameter structures containing microRNA (miRNA), cytokines, chemokines, and other types of proteins that can be internalized by and function within recipient cells. In cancer biology cellular interactions within the microenvironment lead to tumor growth and progression. The most abundant stromal cells within the tumor microenvironment are macrophages and circulating monocytes, recruited into the tumor sites are differentiated into tumor associated macrophages (TAMs) that correlate with a poor prognosis of cancers. Cancer cells derived exosomes contain abundance of miRNAs influencing various stromal cells in the tumor microenvironment and also induce polarization of macrophages with pro- or anti-inflammatory properties. TAMs are also significant source of miRNAs that affect transcriptional activities of different oncogenes or cellular pathway regulators. There are now determined miRNAs for particular cancer type, e.g. miR-16 for breast cancer, miR-21 and miR-29 for NSCLC, miR-155 and miR-301a-3p for pancreatic cancer, miR-21-3p, miR-940, miR-181d-5p, miR-222-3p, miR-125b-5p for ovarian cancer, miR-25-3p, miR-130b-3p, miR-145, miR-203 and miR-425-5p for colorectal cancer, miR-146, and miR-150 for hepatic cancer. In hematological malignancies the cancerogenic role of exosome delivered miRNAs, cytokines and other molecules is identical: evasion of immune surveillance, progression of leukemia (miR-146a, miR-150, miR-155, miR-320) and training the leukemia microenvironment for protecting neoplastic clone with increasing neo-angiogenesis (miR-126, miR-17-92 cluster, miR-210, miR-155, miR-135b). There is a growing interest in clinical applications of EVs (including exosomes) as biomarkers with the identification of the signature miRNAs for specific cancer type and in the development of anti-cancer therapeutics.

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