HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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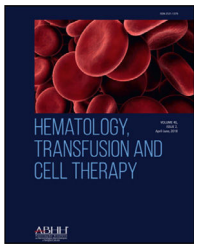

SPEAKER PRESENTATIONS

Sp01

PREDICTORS OF OUTCOME AND SURVIVAL IN PROSTATE CANCER – DATA FROM TERTIARY CARE UROLOGY INSTITUTE IN PAKISTAN

Syed Najeeb Niamatullah

Worldwide prostate cancer is the second most common cancer and fifth in causing cancer mortality in men. It accounts for about 14.1% (more than 1.4 million) of all cancers in men and responsible for 6.8% (about 0.4 million) cancer deaths in the year 2020[1]. In Pakistan, as per Globocan 2020, prostate cancer ranked 13th in new cases (around 4500 cases) and 16th in causing cancer mortality (about 2000 deaths)[2]. This discrepancy might be due to genetic heterogeneity of 220 million population or because of lack of central cancer registry. Over the past decade or so, there is a rapid change in the landscape of treatment of both localized and metastatic prostate cancer. Sophisticated surgical and radiation therapy techniques have reduced the rate of complications with improved quality of life[3]. Use of neoadjuvant, concurrent and adjuvant androgen deprivation therapy with radiation therapy in non-metastatic prostate cancer have shown to improve survival[4]. Novel anti-androgen agents (Abiraterone acetate[5,6] Apalutamide[7] and Enzalutamide[8]) and chemotherapy[9] have also proved clear benefit in castrate sensitive prostate cancer. The arena of radiotheranostics[10] has opened a new frontier in the etreatment of prostate cancer.Clinical features like serum age, ethnicity, PSA levels, Gleason's score[11] and stage at presentation have been shown to effect the prognosis in prostate cancer. Molecular, and genetic factors have been investigated in predicting the outcome in prostate cancer though relatively few are routinely used.

This study will give insight into prostate cancer in our population and help us in making guidelines for better treatment with aim to design the Decision Support Platform (DSP) for artificial intelligence (AI)[12].

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Sp02

GENERIC IMATINIB VS GLEEVEC

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The tyrosine kinase inhibitors (TKI) used in chronic myeloid leukemia (CML) treatment have dramatically changed the disease outcome. Glivec/Gleevec (branded imatinib) was the first TKI developed and has proven to be effective and safe in the long term (Hochhaus et al., 2017).

After the Glivec patent expired, many countries approved generic imatinib for CML treatment. Generic formulations are less expensive and, therefore, more affordable and available for limited resources countries.

Generic formulations of imatinib are used in India since the early 2000s (Parikh et al. 2002) and in most countries since 2016. In Brazil, generics replaced Glivec in 2013 in the first-line treatment patients with CML treated at the Public Health System.

There are still conflicting results about safety and efficacy in the published studies. Regarding pharmacological properties and bioequivalence, several studies compared branded with generic imatinib showing similarity (Malhotra et al., 2014; Arora et al., 2016, Natarajan et al., 2019).

Switching from branded to generic imatinib appears to maintain efficacy and safety (Skazan et al., 2019; Scalzulli et al., 2019; Dalle et al., 2019; Gemelli et al., 2020). However, some studies showed that patients reported new or worsening side effects after switching, primarily mild and moderate, such as nausea, edema, diarrhea, and fatigue (Abudalli et al., 2019, Scalzulli et al., 2020).

In the first-line setting, retrospective and prospective studies compared branded with generic imatinib. A recent study from China compared 236 pts treated with generic with 206 pts treated in first line with branded imatinib and did not find differences in toxicity, responses and overall survival (OS) and progression-free survival in 4 years (Dou, 2020). An updated analysis of a Brazilian study compared the outcomes of a retrospective cohort treated with Glivec with a prospective cohort treated with generics. There was a similar rate of major molecular responses and toxicity at 12 months, OS and PFS survival. (personnal communication).

In terms of health care costs, real-life studies demonstrated that generics use reduced the cost of CML treatment and are more cost-effective than branded imatinib. In the last ELN 2020 recommendations, generic imatinib is indicated as one of the options for first-line treatment in CML, if the drug has quality control of production, similar bioavailability, and efficacy (Hochaus 2020). Monitoring of the short and long-term efficacy and safety is essential.

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Sp03

REVIEW OF NEW INDICATIONS – JOURNAL OF CLINICAL APHERESIS PERSPECTIVE

Huy Pham

Therapeutic apheresis is used to treat various types of disorders. The American Society for Apheresis (ASFA) publishes evidence-based guidelines every 3 years to assist apheresis practitioners in the rationale and management of apheresis patients and outlines basic technical specifications for procedures. However, the ASFA guidelines on the use of therapeutic apheresis published by the Journal of Clinical Apheresis only include indications that have enough evidence in the medical literature to provide apheresis recommendations. The guidelines do not include all the diseases that were reported in the medical literature or the ones that may be potentially treated by apheresis in the future. For new factsheet development, the committee responsible for developing the ASFA guidelines review requests from apheresis practitioners. One or more committee members will evaluate the available literature for evidence for the use of therapeutic apheresis in the disease or indication. A minimum of 10 cases, preferably by at least 2 groups, published in the last decade in peer-reviewed journals. In the current version of the ASFA guidelines (2019), the committee considered several potential new indications; however, none of them had enough evidence to be included in the current guidelines as new factsheets. Of note, the committee will review and issue interim factsheets for new indications if necessary before the release of the next version of the guidelines. Furthermore, due to COVID-19 pandemic, the next version of the ASFA Guidelines will be released in 2023.

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Sp04

HOW I TREAT NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS?

María-Victoria Mateos

Although Multiple Myeloma (MM) remains as a potential incurable disease, important advances are occurring in the knowledge of the disease as well as in the treatment and management and as result, the overall survival is significantly improving. This benefit is applicable along the course of the disease, but the first line of therapy is crucial because almost 100% of patients will receive the first line of therapy and this is the place where patients will get the maximum benefit.

The deeper the response, the longer the progression free and overall survival and patients therefore should receive the combinations of therapies resulting in the highest rates of complete response or undetectable measurable residual disease using sensitive techniques for its detection inside and outside of the bone marrow. This is applicable to both transplant and non-transplant eligible patients and this distinction should be based on biological age together with comorbidities more than in the classical chronological age.

For transplant eligible newly diagnosed MM patients, the treatment should include induction followed by high-dose therapy and autologous stem cell transplantation and maintenance. Induction should include three-drugs based combinations (proteasome inhibitor plus immunomodulatory drug and dexamethasone) and now it is possible to add the monoclonal antibodies targeting CD38 daratumumab to the combination of VTd. Melphalan at high doses followed by transplant has demonstrated to upgrade the response and it results as a complementary rather than an alternative strategy, although in the future risk cytogenetic together with the depth of response will be introduced in the algorithm and some patients could not need transplant. Consolidation might be considered if the response previously achieved could be upgraded and maintenance will be able to maintain the response achieved and under the lenalidomide platform, new combinations are emerging like lenalidomide plus either daratumumab or carfilzomib.

In the setting of transplant ineligible patients, the old standards of care bortezomib, melphalan and prednisone and continuous therapy with lenalidomide and dexamethasone have been replaced by daratumumab plus either VMP or Rd because the addition of daratumumab significantly improved the responses rate including complete responses and undetectable measurable disease but also the outcomes in terms of progression free and overall survival. Bortezomib, lenalidomide and dexamethasone is another combination maybe of choice for fit patients and the platform to which monoclonal antibodies anti CD38 are going to be added.

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Sp05

TREATMENT OF RELAPSED, REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA

Ebru Pekgüç, Burhan Ferhanoğlu

DLBCL represent almost 30% of all non-Hodgkin's lymphoma cases. More than 60% can be cured with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) chemoimmunotherapy. Patients not responding to R-CHOP often have a poor outcome, particularly those with disease refractory to frontline or subsequent therapies. Approximately 10-15% of patients treated with R-CHOP have primary refractory disease (incomplete response or relapse within 6 months after treatment) and additional 20-25% will relapse after an initial response, typically within the first 2 years. Patients with late relapses (>2 years after treatment) have better prognosis. Patients who are eligible to curative therapy should undergo full restaging to fully assess the status of their disease and to assess prognosis. A repeat biopsy at the time of relapse should strongly be considered to ensure that an alternate histology is not present, as an indolent lymphoma has been reported on repeat biopsy in approximately 17% of cases with late relapses. Gene expression profiling has delineated two distinct molecular subtypes of DLBCL: germinal center B-cell like (GCB) and activated B-cell like (ABC); 10-15% of cases are unclassifiable. Detailed analysis of molecular aberrations have led to proposals of new unique, genetically defined subtypes beyond the cell of origin.

Transplant-eligible patients. Treatment with high-dose chemoimmunotherapy and autologous stem-cell transplantation (ASCT) offers the best chance of cure in patients with chemotherapy sensitive relapsed or refractory DLBCL, but due to advanced age and coexisting medical conditions only half of such patients are considered transplantation candidates. Approximately 50% of patients respond to initial salvage therapy and then undergo ASCT, with an overall cure rate of 25 to 35%.

Management of transplant-ineligible patients. While some elderly fit patients may be eligible to ASCT and exhibit comparable outcomes to younger patients, the majority will have comorbidities that will prevent intensive chemo-immunotherapeutic approach. Few prospective trials have been conducted in elderly patients with relapsed/refractory DLBCL. The combination of R-GEMOX and R-bendamustine have been used for paliative purposes. For these cases, new approaches are warranted and new FDA approved drugs will be discussed on new drugs session.

CAR-T cell therapy represents a major paradigm shift in the management of relapsed or refractory DLBCL. Three products, axicabtagene ciloleucil (axi-cel), tisagenlecleusil (tisa-cel) and lisocabtagene maraleucel (liso-cel) are FDA-approved as third line treatment of DLBCL and are commercially available. In pivotal studies, axi-cel, tisa-cel and liso-cel have been associated with overall and complete response rates in the range of 52-82% and 40-54%, respectively, among patients with R/R aggressive B-cell lymphoma. All three agents had characteristic toxicity profile with severe (grade > 3) CRS in 1-22% of patients, and severe (grade > 3) neurotoxicity in 12-28% of patients. Long-term outcome of ZUMA-1 trial recently published and 4 year OS is 41%, median OS is 25.8 months (17), on the other hand in Juliet trial, 5 year PFS is 31%.

Novel therapies. Despite the advance of CAR-T cell therapy, novel therapies are needed. Several agents are FDA-approved for the treatment of R/R DLBCL. **Polatuzumab-Bendamustin-Rituksimab** has received approval based of randomised phase 2 trial involving transplantation ineligible patients with significant improvement rates of complete metabolic response, PFS and OS as compared with BR alone. **Selinexor** has also received approval for patients with R/R DLBCL who have received at least two lines of therapy, as a phase 2 study has shown modest single-agent acitivity. **Tafasitamab** is a humanised anti-CD19 monoclonal antibody with augmented Fc gama receptor afinity. Results from a phase 2 study of tafasitamab combined with lenalidomide showed efficacy, leading to regulatory approval for patients DLBCL ineligible to transplantation.

Bispesific antibodies (bsAbs) refers to an antibody that has binding specificities for two different antigens. A variety of bsAbs are currently under development as therapy for B-cell lymphoma. These bsAbs target CD20 on B-cell and engage T-cells by CD3 in a 1:1 or 2:1 CD20:CD3 Fab format. In general, CRS and neurotoxicity are significantly less frequent than observed with CD-19 directed or blinatumomab therapies. In R/R DLBCL, ORR range from 37 to 90% with CRR from 19 to 55%. However, follow-up for these new bsAbs is short and the durability of responses remains to be established.

Loncastuximab tesirine is a CD-19 directed antibody-drug conjugate. It has substantial single-agent antitumour activity and produces durable responses with an acceptible safety profile. 145 patients were enrolled with diagnosis of R/R DLBCL including high-risk characteristics for poor prognosis such as double-hit, triple-hit, transformed or primary refractory DLBCL. ORR was 48% with 24% CR rate, potencially offering a new therapeutic option for heavily pre-treated patients with R/R DLBCL.

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Sp06

HAPLOIDENTICAL VERSUS UNRELATED ALLOGENEIC STEM CELL TRANSPLANTATION FOR ADULTS WITH ACUTE LEUKEMIA

Arnon Nagler

Allogeneic hematopoietic cell transplantation (HSCT) remains an important curative treatment modality for patients with high risk acute leukemia (AL) (1). A matched unrelated donor (MUD) or a haploidentical related donor (Haplo HSCT), are both valid options in the absence of a fully HLA-matched sibling donor (MSD) for HSCT in AL. In my presentation I will present and discuss focusing on the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) registry based studies in recent few years (2-6) comparing MUD and Haplo HSCT for both acute

myelogenous leukemia (AML) (2-3) and subsequently acute lymphoblasic leukemia (ALL) (4-7) addressing various aspects including type of grafts,conditioning regimens, GVHD prophylaxis and others in patients in remission and well as in those with active disease (2-7). In large our studies have shown comparable outcome including leukemia-free (LFS), overall survival (OS) and graft versus host disease (GVHD) free (Rel) free survival (GRFS) after Haplo-HSCT mostly with post transplantation cyclophosphamide (PTCy) versus MUD allo-HCT. Haplo HSCT with PTCy was usually associated with low transplant related mortality (7) and reduce incidence of chronic GVHD especially with bone marrow (BM) grafts (2). Moreover, Haplo HSCT associated TRM versus MUD associated TRM, impressively reduced with time (7) and results in ALL improved with time (6). As for the relapse rates and the graft versus leukemia (GVL) effect although still controversial, some of the data indicate lower Rel which may speak for stronger GVL afrer Haplo HSCT.

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Sp07

GVHD TREATMENT

Elif BirtaşAteşoğlu

Graft Versus Host Disease (GVHD) is the condition that occurs when immune cells transplanted from the graft recognize the host as foreign and initiates an immune reaction that causes disease in the transplant recipient. GVHD is divided into acute and chronic GVHD (cGVHD) based on the time of onset using a cutoff of 100 days. However, signs of acute and chronic GVHD may occur outside of these periods.

The choice of initial treatment for acute GVHD depends on the organs involved, the severity of symptoms, the prophylactic regimen used. The severity of acute GVHD is determined by an assessment of the degree of involvement of the skin, liver, and gastrointestinal tract. Grade I GVHD defines cutaneous GVHD over ≤50 percent body surface area without liver or gastrointestinal tract involvement. Grade I GVHD is managed with topical treatments such as topical steroids. Patients with Grade II or higher GVHD are treated with systemic glucocorticoids and nonabsorbable oral steroids are added for patients with gastrointestinal involvement. The most commonly used glucocorticoid is methylprednisolone with a dosage of 2 mg/kg per day. Patients whose GVHD progress by day 5 or who do not respond by day 7 are considered as corticosteroid resistant. For patients with glucocorticoid-resistant acute GVHD, participation in a clinical trial is recommended. If no trial is available, ruxolitinib,

mycophenolate mofetil, etanercept, extracorporeal photopheresis, anti-thymocyte globulin, alpha-1 antitrypsin, mesenchymal stromal cells, everolimus, or sirolimus can be used.

Clinical manifestations of cGVHD may be restricted to a single organ or widespread. The primary manifestations are skin involvement resembling lichen planus or cutaneous scleroderma, dry oral mucosa, ulcerations and sclerosis of the gastrointestinal tract, elevated serum bilirubin, and bronchiolitis obliterans. First-line treatment of cGVHD consists of steroids. For patients with mild cGVHD, localized/topical treatment can be preferred rather than systemic therapy. For initial treatment of moderate or severe cGVHD, systemic treatment with prednisone or methylprednisone at an initial dose of 1 mg/kg body weight/day should be used. The addition of azathioprine, mycophenolate mofetil, cyclosporine, thalidomide, or hydroxychloroquine to prednisone did not improve the response rate or other end-points in randomized trials. If symptoms progress during the first 4 weeks of first-line therapy or there is no improvement in symptoms within 8–12 weeks, second-line therapy should be initiated. For steroid refractory cGVHD patients ruxolitinib can be added to prednisone. Non-pharmacologic therapies such as extracorporeal phopheresis (ECP) has the advantage of being non-immunesuppressive. An immunosuppressive drug can be added to prednisone such as a calcineurin inhibitor or mycophenolate mofetil, but none shown to be effective. İbrutinib which is an inhibitor of Bruton's tyrosine kinase (BTK) has activity against cGVHD.

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Sp08

EVOLUTION OF THE PLEURAL SECRETOME ASSOCIATED WITH PLEURAL METASTASIS

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James D. Luketich, MD, Ibrahim Sultan, MD,
Vera S. Donnenberg, PhD

Malignant pleural effusions (MPE) are characterized by a distinct and complex secretome that varies little between malignancies. To understand the origin and functional significance, we measured 40 cytokines and chemokines in 356 MPE (mainly breast cancer, lung cancer and esophageal cancer), and compared them to benign effusions (n=18) and normal, non-effusate pleural fluid (n=27).

Pleural effusions were collected during therapeutic drainage. Normal (non-effusate) pleural fluid was aspirated during minimally invasive cardiac surgery. Samples were clarified by centrifugation and stored at -80°C until assay. Samples were analyzed with the Luminex platform, using the MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel - Premixed 38 Plex (Cat. No. HCYTMAG-60K-PX38), plus IL-6Rα (Cat. No. HANG2MAG-12K-01), and TGFβ (Cat. No. TGFBMAG-64K-01).

The baseline secretome in normal pleural fluid is dominated by IL-6Rα, CCL2, CXCL10, FGF2, TGFβ1 and CCL22. Effector cytokines (IFNα, IFNγ, CCL3, TNFα and TNFβ) and most stimulatory cytokines (GM-CSF, TGFα, G-CSF, IL-2, IL-5, IL-7, IL-9, IL-12p40, IL-12p70, IL-3) were absent in NPF.

Benign effusions, whether due to cardiac insufficiency or chronic inflammation (asbestosis without malignancy) resulted in a profound secretomic change, with statistically significant increases in IL-6, TGFβ1, GRO, IL-10 and IL-8, and decreases in FGF2 and IL-15.

All cytokines and chemokines present at elevated levels in benign effusions were also elevated in malignant effusions, with statistically significant increases in G-CSF, CX3CL1, GM-CSF, IFNγ, IL-1TNFα, IL1Rα, CCL4, VEGF, TNFβ, EGF, IFNα, IL-4 and IL-12p40, compared to benign pleural effusions.

Benign effusions can result from an imbalance between hydrostatic and oncotic forces or from inflammation. In both conditions our data indicate a dramatic and consistent change in the pleural environment dominated by IL-6, a highly pleotropic cytokine. When bound to sIL6-Rα, IL-6 induces pro-inflammatory trans-signaling that is markedly stronger than classic signaling and a potent driver of the epithelial to mesenchymal transition (EMT). Additionally, CXCL10, IL-8 and TGFβ1 are known to promote EMT, critical for the maintenance of the normal mesothelium, but dangerous when cancer cells reach the pleural environment, because EMT is associated with cell motility, invasion and therapy resistance.

It is unknown whether prior perturbation of the pleural environment is prerequisite to pleural metastasis, or alternatively, whether chance seeding of the pleura with metastatic tumor leads to secretomic changes similar to those seen benign effusions. In either case, the pleural environment is conditioned to promote tumor growth and inhibit anti-tumor immunity. The presence of cytokines such as VEGF and FGF2 in MPE further condition the pleural environment for tumor growth. The contained nature of the pleural space suggests that local interventions with protein therapeutics to block or augment key cytokines may alter this environment and render pleural metastases susceptible to chemo- or immunotherapy.

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Sp09

INTRAPLEURAL THERAPY TO DRIVE SYSTEMIC ANTI-TUMOR IMMUNITY

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Cancer metastatic to the pleura is uniformly fatal with a median survival of six months and quality of life that is diminished by dyspnea and discomfort. There is currently no curative treatment once metastatic disease has occurred. Current standard of care treatment for malignant pleural effusions (MPE) is exclusively palliative, consisting of drainage, followed by systemic therapy (chemotherapy, endocrine, or immunotherapy). Our institutional experience with systemic immune checkpoint blockers indicates a marginal

improvement in overall survival in a small subset of patients. Clearly, the incidence of MPE and lack of effective treatments has created an urgent unmet need to develop an effective treatment.

Our studies of the pleural secretome in non-small cell lung cancer and mesothelioma, as well as extensive secretomic data in MPE from other cancers, indicate that the IL-6/IL-6Rα axis is prominent in pleural effusions and drives the epithelial to mesenchymal transition (EMT). We have identified additional cytokines that are absent in normal pleural fluid but prominent in malignant effusions. We have also found that MPE T cells, removed from their environment, are capable of expansion in culture, polyfunctional cytokine response, and are cytolytic to autologous tumor. Because the pleural space is lined with mesothelial cells joined by tight junctions, we hypothesize that it acts as a cytokine-rich bioreactor which promotes EMT in cancer cells metastatic to the pleura, and redirects the abundant immune infiltrate to promote, rather than inhibit, tumor growth. We hypothesize that as a master cytokine, IL-6 and its soluble receptor drive this process. Therefore, local blockade of sIL-6Rα will alter the pleural cytokine milieu, inhibiting aggressive tumor behavior and promoting anti-tumor immune response. Once unleashed in the pleural space, tumor-specific T cells could be expected to migrate to the periphery through the draining lymphatics and respond to extra-pleural metastases. Further, based on our current data, we are confident that the 100 million MPE T cells that are routinely recovered during routine therapeutic MPE drainage can be expanded in culture for an adoptive cellular therapy product that is faster, better and cheaper than conventional solid-tumor derived culture-expanded tumor infiltrating lymphocytes (TIL).

What remains to be determined is whether blockade of dominant cytokines in MPE together with anti-PD-1/PD-L1 therapy can condition the pleural environment sufficiently to support and expand the existing anti-tumor responses.

Combining the knowledge derived from these studies we propose to devise a personalized combined treatment strategy that conditions the pleural environment without incurring systemic toxicities and facilitates local and systemic anti-tumor immune response.

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Sp10

CAR T-CELL

Francesco Saglio

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.

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, adult patients affected by Non-Hodgkin Lymphomas and more recently adult patients affected by Multiple Myeloma 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 commercially available CAR-T cells has increased the number of patients treated by this cell therapy products and has also permitted to confirm their safety and efficacy profile in the "real life".

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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Sp11

TARGETED THERAPY IN AML TREATMENT

Giovanni Martinelli

Prof. Martinelli will speak about new drugs in the treatment of acute leukemias, starting from mechanisms of actions of the compounds and explaining strategies for clinical research.

Venetoclax is a bcl-2 inhibitor that is entering in the therapy of AML. The use of venetoclax will be explored with particular attention to combination with purine and pyrimidine analogs and metabolism.

Ponatinib is a pan TKI with particular activity on BCR-ABL1 fusion protein, VEGF and FLT3, and a high number of collateral activity on immunogenic cell death and environment. Ponatinib is able to protect against the emergence of BCR-ABL1 mutations. Ponatinib was used in new-onset and relapse-refractory Ph+ ALL. The use of ponatinib may be further expanded in Ph-like/3C-UP ALL and in subcategories of AML.

Gilteritinib is an FLT3, AXL, and ALK inhibitor with single-agent activity in R/R AML. Gilteritinib multikinase inhibition and differentiation effects will be explored, together with combination with chemotherapy.

MDM2 and Menin inhibition are appealing strategies in the treatment of predefined subsets of AML, preliminary laboratory data will be presented.

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Sp12

HAEMOPHILIA AND NURSING CARE

Marcela Ganzella

Hemophilia is a rare, inherited, X-chromosome-linked bleeding disorder resulting from a deficiency of clotting factor VIII (hemophilia A) or factor IX (hemophilia B). In the world, according to the World Federation of Hemophilia 2019, there are currently approximately 157,517 people diagnosed with Hemophilia A and 31,997 Hemophilia B. Nurses may be involved in providing direct clinical care, education, support and self-management for patients and their families. In this presentation we will talk about important aspects of hemophilia: pathophysiology, nursing care and concern, treatment pathway and patient education

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Sp13

RHABDOMYOSARCOMA

Mehmet Fatih Okçu

Rhabdomyosarcoma is the most common soft tissue sarcoma in childhood. While based on the cooperative group work from US and Europe diagnosis and treatment guidelines exist management controversies exist for newly diagnosed intermediate and high risk disease and in patients with relapses. The presentation will discuss further details on management of these patient groups in the light of recent published work.

Non-rhabdomyosarcomatous soft tissue sarcomas (NRSTS)

NRSTS are large group of heterogenous group of soft tissue sarcoma diagnoses representing half of all childhood soft tissue sarcomas. In this presentation we will review standard approach in general on diagnosis and management of soft tissue tumors and further discuss how recent molecular work informs diagnosis and management of subgroup of patients.

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Sp14

THE APPROACH AND DIAGNOSIS OF COOMBS NEGATIVE HEMOLYTIC ANEMIAS

Achille Iolascon

Anemia affects 1.6 billion of people worldwide, about 10% of these individuals are affected by rare anemias of which 80% are hereditary.[1] Hereditary anemias (HA) embrace a highly heterogeneous group of disorders characterized by anemia of variable degree and by complex genotype-phenotype correlations. Differential diagnosis, classification, and patient stratification among HA are often very difficult.

To date, the major current application of next generation sequencing (NGS) in diagnostics is through disease-targeted tests for which multiple causal genes are known. Some studies have already demonstrated the utility of targeted-NGS (t-NGS) approach in the study of specific subtypes of HA patients. Here, we described the diagnostic workflow based on t-NGS that we developed for the diagnosis of patients affected by HA. Within this wide group of disorders, we included: (1) hyporegenerative anemias, as congenital dyserythropoietic anemias (CDA); (2) hemolytic anemias due to red cell membrane defects, as hereditary spherocytosis (HS) and stomatocytosis (HSt); hemolytic anemias due to enzymatic defects, as pyruvate kinase (PK) deficiency.[1–5]

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