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Speaker Presentations

SP-001

EUROPEAN LEUKEMIA NET RECOMMENDATIONS FOR CHRONIC MYELOID LEUKEMIA

Rüdiger Hehlmann. *Medizinische Fakultät Mannheim der Universität Heidelberg*

- Imatinib, dasatinib, nilotinib equally recommended 1st-line
- Slightly more early progressions, but safety advantage with imatinib
- Response with high dose imatinib similar to that with 2G-TKI
- 10-year survival with imatinib 85%
- 10-year molecular responses with imatinib: MR[2] 92%, MMR 89%, MR[4] 81% MR[4.5] 72%, MR[5] 59%
- Monitor response, toxicity and compliance
- Dasatinib, nilotinib, bosutinib, ponatinib recommended 2nd and 3rd line
- Early SCT may be an option for high risk CML

SP-002

POTENTIAL TOXICITY OF IRON OVERLOAD: AN INDICATION FOR IRON CHELATION IN LOW RISK MYELODYSPLASTIC SYNDROME AS WELL AS BEFORE AND AFTER BMT

Eliezer Rachmilewitz. *Hematology Department, E. Wolfson Medical Center, Holon (Israel)*

Iron overload (IO) is the consequence of hemolysis, blood transfusions and increased iron absorption. Despite a very efficient regulation of iron absorption and excretion, the body has no way to get rid of excess iron, which is stored in major organs such as liver, spleen, pancreas, endocrine glands and mainly in the heart.

The potential toxicity of IO is becoming more and more recognized, mainly due to the identification and understanding the deleterious effects of free iron species – Non Transferrin Bound Iron (NTBI), its chemically labile component Labile Plasma Iron (LPI) which can permeate into the cell and intracellular Labile Iron Pool (LIP). Their presence results in generating reactive oxygen species (ROS), particularly the OH- radical, which can oxidize and consequently destroy almost every cellular compartment including DNA, particularly in erythroid precursors.

Myelodysplastic syndromes (MDSs) are characterized by ineffective hematopoiesis, peripheral blood cytopenias, and potential for malignant transformation to leukemia. Lower/intermediate-risk MDSs such as refractory anemia (RA) and refractory anemia with ring sideroblasts (RARS) are associated with longer survival and high red blood cell (RBC) transfusion requirements resulting in secondary IO such as thalassemia.

From the evidence in other transfusion dependent anemia such as thalassemia, it is quite clear that IO is a major factor inducing morbidity and mortality.

Therefore, there is a clear cut indication to treat IO, and mainly to prevent the accumulation of the free iron species (LPI and LIP) in the plasma and in the cells by using iron chelators.

There are two oral iron chelators – Deferasirox (DF) and Deferriprone (DFP). In multitransfused MDS with RA and RARS patients, there is increasing number of reports of retrospective analysis of iron chelation with DF demonstrating prolonged survival. However, one must bear in mind that DF may cause several side effects mainly in the gastrointestinal tract and an increase in creatinine.

Until now, there are only few reports on the use of DFP in MDS. There are still no data on prospective study on the effects of iron chelation on survival of patients with MDS.

Another potential way to prevent excess iron absorption is by increasing the levels of the peptide hormone hepcidin, which is a negative regulator of body iron via erythroferrone,, induced by ineffective erythropoiesis. Moreover, iron depletion by iron chelators may induce terminal differentiation of leukemic cells in addition to reduced parameters of oxidative stress including DNA oxidation, in peripheral blood cells of patients with MDS. These findings suggest their potential use in treating/preventing/delaying the transformation of MDS to acute myeloid leukemia.

In addition, there are several reports demonstrating a direct relationship between prolonged survival and mortality of MDS patients with the extent of IO before, during and after bone marrow transplantation (BMT).

In conclusion, better understanding of ineffective erythropoiesis, iron metabolism and IO, will provide more convincing evidence on the potential benefit of iron chelators in low risk MDS patients.

SP-003

CHIMERIC ANTIGEN RECEPTOR-ENGINEERED T CELLS: WHERE ARE WE NOW AND WHERE ARE WE HEADED?

Saar Gill. *Hospital of the University of Pennsylvania*

On July 1, 2014, the United States Food and Drug Administration granted 'breakthrough therapy' designation to CTL019, the anti-CD19 chimeric antigen receptor (CAR) T-cell therapy developed at the University of Pennsylvania. This is the first personalized cellular therapy for cancer to be so designated and occurred 25 years after the first publication describing genetic redirection of T cells to a surface antigen of choice. At last count more than 70 clinical trials using CAR T cells, most of them targeting CD19, were actively recruiting patients in North America, Europe, and Asia. Patients

with high-risk B-cell malignancies are the first beneficiaries of an exciting and potent new treatment modality that harnesses the power of the immune system as never before. These patients represent the vanguard of enormous preclinical efforts to develop CAR T-cell therapy into a procedure that we hope will one day be routine, definitive and curative.
In this presentation, I will explain the concept of CAR T cells, describe the extant results in hematologic malignancies, and share my outlook on where this modality is likely to head in the near future. I will also outline the vital contributions made by the correlative science laboratory to understanding the kinetics of T cell proliferation and the magnitude of tumor response, as well as in diagnosing the cytokine release syndrome, an important toxicity of CAR T cell therapy.

SP-004
ACUTE LYMPHOCYTIC LEUKEMIA: CURRENT AND FUTURE THERAPEUTIC STRATEGIES

Dieter Hoelzer. *Goethe University Hospital*

For an adequate treatment of adult acute lymphoblastic leukemia, a prerequisite is a precise diagnosis.
Diagnostic measures: This should include morphology, immunophenotype, cytogenetics, to confirm not only the diagnosis of ALL, but to determine the different ALL subsets.
New genetic and molecular markers are recommended to detect rare subtypes, such as the recently discovered Ph-/bcr-abl-like ALL, and the Early T-precursor (ETP) ALL.
Risk stratification and prognostic factors: For adult ALL it is essential to define patients as Standard or High Risk patients. The risk stratification is currently determined by a combination of prognostic factors at diagnosis and treatment-related parameters.
Minimal Residual Disease evaluation during therapy is now the most relevant prognostic parameter for treatment decisions.
Treatment: The backbone of treatment is still the chemotherapy, including and induction therapy of ~1-2 months, consolidation cycles for 6-8 months. The maintenance should contain high dose-methotrexate (HD-MTX), or high dose-cytarabine (HD-AraC), as well as asparaginase, the only ALL-specific drug, either in its native or, more recently, in its pegylated form (PEG-asparaginase).
Targeted therapy with tyrosine kinase inhibitors (TKI) in Ph+ ALL: The TKIs should be combined with chemotherapy immediately from the diagnosis. Imatinib (400-800 mg/d) is the TKI with the most experience, but there is an increasing number of studies with the 2nd generation TKIs dasatinib and nilotinib.
Most often, mutations are the reason for resistance. For this situation, 3rd generation inhibitors, such as ponatinib, are indicated.
The aim of the continuous treatment is to achieve a bcr-abl-negativity. The TKI should be also applied after stem cell transplantation and during maintenance therapy.
Stem cell transplantation: Allogeneic stem cell transplantation from a related or unrelated donor is the treatment of choice for adult High Risk ALL patients in CR1, for elderly patients also reduced intensity conditioning (RIC) can be considered.
Auto-SCT is a new option for patients being MRD-negative.
Haplo-SCT is, because of the availability of donors for nearly all patients, the fast realisation, and the so-far low complication rate, currently explored in several studies.
Antibody therapy: Antibody therapy is a very promising new option in adult ALL.
Anti-CD20 rituximab in combination with chemotherapy is strongly recommended for Burkitt leukemia/lymphoma. The anti-CD22 immunoconjugates directed against CD22 are effective in refractory/relapsed ALL, but also in frontline, when combined with a low intensity-chemotherapy.
There are also new approaches to activate the patients' own T-cells to target the leukemic cells;
The first is the bispecific antibody directed against CD19/CD3 blinatumomab, effective in refractory/relapsed ALL, but even more in the patients being MRD-positive.
An exciting new option are the Chimeric Antigen Receptor modified T (CAR T) cells directed against CD19, with convincing results in several studies, but need confirmation in larger series.

SP-005
DIAGNOSTIC AND PROGNOSTIC MARKERS IN ACUTE LYMPHOBLASTIC LEUKEMIA

Monica Messina. *Division of Hematology, Department of Cellular Biotechnologies and Hematology, "Sapienza" University, Rome, Italy*

Acute lymphoblastic leukemia (ALL) is a lymphoid neoplasm characterized by the clonal accumulation of B- or T-lineage precursor in the bone marrow.
Despite the introduction of avant-garde molecular techniques, the ALL diagnostic workflow still relies on the combination of gold-standard techniques: morphology, immunophenotype, conventional cytogenetics and molecular analyses, that also allow the subclassification of ALL.
Beyond cytomorphology - that is still indispensable for a correct diagnosis - and flow cytometry, crucial to define cell lineage and developmental stage, the diagnostic assessment includes conventional cytogenetics, FISH or reverse transcriptase PCR that confirm subtype classification and bear also important prognostic implications (see below).
Prognostic stratification at diagnosis is based on multiple parameters. Traditional risk factors include age, gender, white blood cell count (WBC), immunophenotype, chromosomal rearrangements. In particular, elderly patients (>60 years) and infants have a dismal prognosis; in addition, male gender, high WBC count - >30×10^9/L in B-lineage ALL (B-ALL) and >100×10^9/L in T-lineage ALL (T-ALL) - are adverse prognostic factors. Among the most recurrent chromosomal abnormalities detected in B-ALL, *MLL* rearrangements, t(9;22)/*BCR-ABL1*, t(17;19)/*TCF3-HLF*, near haploidy and low hypodiploidy are associated to a high-risk disease while t(12;21)/*ETV6-RUNX1* and high hyperdiploidy are acknowledged as good prognostic biomarkers. In T-ALL, the majority of cytogenetics abnormalities lead to the ectopic expression of transcription factors (i.e. *TAL1*, *LMO1*, *LMO2*, *TLX1* and *TLX3*) that interferes with lymphoid differentiation. However, their dysregulation do not impact on outcome or their prognostic significance is still controversial.
A pivotal role in the management of ALL patients, during and after therapy, is currently represented by the evaluation of minimal residual disease (MRD), conventionally performed by tracking the residual leukemic cells by flow cytometry looking for the leukemia-specific immunophenotypic profile or by quantitative PCR, that achieves a higher sensitivity, targeting specific Ig/TCR rearrangements or fusion transcripts. MRD quantification is at present the most powerful prognostic factor that permits the proper assignment of patients to risk groups and treatment arms, accordingly. A further improvement in MRD assessment might arise from the introduction of high-throughput technologies (i.e. next-generation sequencing, droplet PCR and multidimensional flow cytometry), that are currently under intense investigation.
With the advent of microarray and sequencing high-throughput technologies, a plethora of novel genetic alterations emerged with some of them displaying a potential predictive role. In B-ALL, an adverse prognostic impact has been ascribed to *IKZF1* deletions, *CRLF2* rearrangements, iAMP21, JAK/STAT pathway mutations; contrariwise, ERG deletions predict a favorable outcome in children. Also, novel ALL subgroups have been identified. Within B-ALL, it is worth mentioning the *BCR-ABL1*-like subtype: though lacking *BCR-ABL1*, these cases carry a wide range of genetic alterations that lead to a deregulated tyrosine kinase and/or cytokine receptor signaling. *BCR-ABL1*-like ALL is characterized

by high-risk clinical features and poor outcome, though it seems to lose its predictive role in pediatric MRD-oriented protocols. Beside the novel recurrent mutations and copy number aberrations affecting *NOTCH1*, *BCL11B*, *FBXW7*, *MYB*, *PTEN*, *RB1*, the classification of T-ALL have been greatly refined with the recognition of Early T-cell precursor (ETP) cases that exhibit a gene expression profile similar to hematopoietic stem cells coupled to an immature immunophenotype with a reduced expression of T-cell markers and the aberrant expression of myeloid/stem cell antigens. Though traditionally regarded as a high-risk subtype, the outcome of ETP ALLs seems improved by the current risk-adapted approaches.

Lastly, *CREBBP* mutations in B-ALL and *NT5C2* in T-ALL are frequently found at relapse and associated to resistance to glucocorticoid and thiopurines, respectively.

These additional layers of complexity open new issues. Indeed, the current challenges stand in the incorporation of the novel biomarkers in the routine diagnostic/prognostic workflow and in developing new algorithm that integrates genetic risk factors with MRD evaluation.

SP-006

DEBATE: IN PH-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA, DE WE NEED CHEMOTHERAPY IN INDUCTION THERAPY?

Josep-Maria Ribera. *Clinical Hematology Department. ICO-Hospital Germans Trias i Pujol, Josep Carreras Research Institute, Badalona, Universitat Autònoma de Barcelona, Spain*

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Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) accounts for 5% of ALL in children and 25% in adults. This frequency rises to 40%-50% in patients older than 60 years. As compared to the pre-imatinib era complete remission (CR) rates have improved from 60%-70% to 85%-95% in relatively small non-randomised studies, most of which simply added imatinib to their previous standard chemotherapy regimens, with survival reaching approximately 50% compared with ≤20% in the pre-imatinib era. Younger patients usually receive allogeneic hematopoietic stem cell transplantation (alloHSCT) with standard myeloablative conditioning (MAC). There is general consensus on the use of prophylactic imatinib maintenance to prevent post-SCT relapse after MAC-SCT.

Several studies using imatinib or dasatinib combined with steroids have shown an impressive 95-100% CR rate in elderly patients with Ph+ ALL, and similar results have been observed in recent studies with dasatinib or nilotinib combined with less intensive chemotherapy. The low toxicity associated with these regimens has allowed alloHSCT to be performed with reduced intensity conditioning in a subset of these patients, with promising results. These results have raised the question as to the optimal thyrosine kinase inhibitor (TKI)/chemotherapy front-line combination that could be offered to young patients before alloHSCT. To date, there is no comparative study evaluating second-generation TKI (nilotinib, dasatinib) *versus* imatinib as first-line treatment. Induction therapy, which is most commonly based on TKI with less or even no chemotherapy, should probably be preferred to standard intensive chemotherapy/TKI combinations. The Spanish PETHEMA Group has shown an improvement in event-free survival by increasing the dose of imatinib and reducing the amount of chemotherapy during induction and consolidation compared with a historical trial. More convincingly, in the GRAAPH-2005 randomized trial the French GRAALL Group has demonstrated lower early mortality and a higher CR rate in patients receiving imatinib combined with less-intensive chemotherapy compared with those receiving HyperCVAD/imatinib, with equivalent results after alloHSCT. Once CR has been reached, autologous HSCT might also be a good option, at least in patients who have achieved good molecular response, or in those who cannot tolerate alloHSCT.

The third-generation TKI ponatinib is currently the only option for patients progressing with the T315I mutation. However, promising preliminary results have been reported with the combination of ponatinib and HyperCVAD as front-line therapy for patients with Ph+ ALL, and several trials are currently evaluating the combination of ponatinib with less intensive chemotherapy schedules. Finally, the improving results attained with the new immunotherapeutic approaches in relapsed or refractory ALL will lead to evaluation of the combination of these agents with TKI as possible chemotherapy-free combinations for treating newly diagnosed patients with Ph+ ALL.

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SP-007

ACUTE MYELOID LEUKAEMIA: CURRENT AND FUTURE THERAPEUTIC STRATEGIES

Alan K. Burnett. *CTI Life Sciences, Seattle USA*

Acute Myeloid Leukaemia (AML) is a heterogeneous disease from the morphological, immunophentotypic, cytogenetic and molecular perspectives. All can be used as positive or negative prognostic markers, a few of which have found use as predictive to specific therapies. Some of the molecular lesions have become targets for therapy (such as FLT3/ NPM1c) but so far there is a lack of randomised data to show that such targeted therapy improves survival.

The first clinical decision is whether a patient should receive an intensive approach to therapy or a non-intensive alternative. This question predominantly arises in patients over 70 years, and/or those with co-morbidities. There is also increasing recognition that some patients with adverse disease characteristics may derive little benefit from an intensive approach. For such patients a more gentle therapy is justifiable (e.g. demethylation therapy or low dose Ara-C)

Induction with Ara-C and an anthracycline (e.g. daunorubicin at a dose of 60 mg/m^2) is standard but many variations have been assessed (addition of a third drug, dose variation etc) without convincingly changing outcome. There is recent and ongoing interest in adding cladrabine, or using an alternative like FLAG-Ida, while a meta-analysis suggests that addition of

the immunoconjugate, gemtuzumab ozogamicin (GO) improves survival in favourable and intermediate risk group, in each case, not by improving remission rate, but rather by reducing relapse risk.

Higher doses of Ara-C monotherapy as consolidation in younger patients is well validated, but the actual dose does not have to be the traditional 3 mg/m^2 since a 1.5 mg/m^2 has produced similar results. It is also of limited benefit in adverse risk patients where there are better alternatives such as FLAG-Ida. The question is how many courses are required. This may vary by risk group but the UK studies suggest a maximum of 2 courses, and a randomisation of 1 vs 2 has been completed. In older patients who respond well to induction, there does not seem to be benefit in more than 1 consolidation. Allogeneic transplant SCT from a sufficiently matched donor after myelo-ablative conditioning is clearly the most effective way to prevent relapse, but it has associated intractable morbidity and mortality. One of the limitations of this approach is the lack of survival benefit in patients >40 years, but reduced intensity conditioning represents and alternative with recent evidence that intermediate risk patients derive survival benefit, but in the same series adverse risk do not. There is continuing "discussion" about which younger patients need SCT in CR1. It is generally agreed that favourable risk do not, and adverse risk do, but the question is who in the intermediate risk group benefits. FLT3 status is often used, but just as mutations confer an adverse risk for chemotherapy, so they appear to do for transplant, however those which are not "protected" by an associated NPM1c (about 10% of intermediate risk) benefit from SCT.

Molecularly targeted therapies against FLT3 and to a limited extent in other mutations are in development but have either failed to show survival benefit in randomised studies, or have not reached randomised assessment. One of the outstanding successes is the development of the "chemo-free" treatment of acute promyelocytic leukaemia (APL) with ATRA and Arsenic which delivers a survival >90%.

There is much interest in what role minimal residual disease (MRD) monitoring may have in prognostics and guiding therapy. MRD+ve generally (but not always) means imminent relapse and as such give a patient-specific risk rather than an average as in current factor use. The range of PCR based assays is more limited than multiparameter immunophenotyping. The latter suggests that on reaching CR 50% are MRD +ve and in older patients, at least, this is the most important prognostic marker in multivariable analysis. The crucial question is how to react therapeutically. In other diseases this has been an indication that treatment may be de-escalated in the MRD-ve cases and intensified in the MRD+ve. However such evidence as is available in AML suggests that there may be more to gain is intensifying the MRD-ve. There is also the question of whether there is benefit in therapeutic intervention at the stage of MRD positivity rather than at the time of frank relapse. This needs prospective randomised assessment.

SP-008

AML IN THE "ELDERLY" PATIENT

Charles A. Schiffer. *Professor of Medicine and Oncology, Joseph Dresner Chair for Hematologic Malignancies, Chief, Multidisciplinary Leukemia/ Lymphoma Group, Wayne State University School of Medicine, Karmanos Cancer Institute*

The outcome of treatment of older adults with acute myeloid leukemia (AML) remains unsatisfactory, although certainly not a totally futile exercise. Patients satisfying the entry criteria for cooperative group clinical trials can be expected to have complete remissions (CR) rates of 50-55%, with CR durations of ~ 9 months, albeit with long term survival of only ~ 10%. There has been relatively little overall improvement in decades. Nonetheless, there is considerable benefit from achieving CR, not the least of which is being at home for months with safe blood counts permitting normal activities.

Even so, many oncologists, including those who readily treat patients with advanced solid tumors and compromised performance status, are reluctant to offer potentially remittive chemotherapy to older patients with AML. One consideration of course, is the need for 3-4 weeks of hospitalization with the possibility that the patient may not survive and ever leave the hospital. However, advances in supportive care, most notably the development of highly effective antiemetics and replacement of the debilitating and nephrotoxic amphotericin B with the more tolerable imidazoles, have permitted safer delivery of myelosuppressive chemotherapy such that the expected 30 day mortality is now ~10%.

The traditional breakpoint between younger and older (sometimes pejoratively termed "elderly") patients, had been between ~60 years of age, probably deriving from historical cutoffs for the application of allogeneic transplantation. Although it is true that the frequency of poor prognostic factors such as higher risk cytogenetics, overexpression of multidrug resistance proteins and AML evolving from prior myelodysplasia increases in older individuals, it is silly to assume that there are dichotomous differences in leukemia biology according to discrete boundaries in patient age. In addition, age alone is not a reliable surrogate for the ability to tolerate induction chemotherapy and it is likely that subjective assessments of "performance" can be enhanced by the use of recently developed comorbidity indices. Thus, for patients with adequate baseline medical status and organ function, almost irrespective of age, the first instinct should be to consider standard induction therapy or a well-conceived clinical trial. Standard induction therapy should always be considered in the occasional older patient with "favorable" karyotypes (core binding factor AML – t(8;21) or abn16q22) or nucleophosmin1 (NPM1) mutations.

The real dilemma concerns patients who are truly "elderly", regardless of their exact age, as evidenced by the presence of serious medical and/ or cognitive co-morbidities. Supportive approaches with transfusion and hydroxyurea are suitable for some such patients. There are many other older patients however, who are otherwise reasonably well and functional and who could benefit from therapies with the more modest aim of improvement in blood counts. The hypomethylating agents, 5-azacytidine and decitabine, and, particularly in Europe, low dose cytarabine, all of which can be administered in the outpatient setting, are now used frequently in this setting. These agents produce very low rates of CR and variable rates of "hematologic improvement", albeit with the potential for significant cytopenias and hospitalizatiom as well as the need for multiple courses of therapy. There have been no randomized trials comparing these putatively "gentler" approaches with standard anthracycline/cytarabine induction therapy.

When considering this decision, it should be noted that AML in olderly patients can present in a couple of different "flavors":

- "proliferative" AML with hypercellular marrows and rising levels of peripheral blasts
- "MDSy" AML (with or without a prior diagnosis of MDS) with > 20-30% blasts but with slowly progressive cytopenias

The former requires an almost immediate decision about the suitability of intensive induction therapy, while many of the latter patients may not require any treatment, other than perhaps red blood cell transfusion, for long periods of time. It is likely that patients with more slowly proliferative disease are over-represented in the trials using hypomethylating agents and low dose cytarabine and one should be cautious in extrapolating even these modest outcomes to the more general population of older patients with AML.

The treatment of less fit older patients has become an active area of clinical research. Portrayed as an "unmet medical need" and a potentially easy target because of the historically poor results, multiple pharmaceutical companies have designed small, sometimes phase 2 trials in an attempt to get new drugs approved without directly challenging the standard of anthracycline and cytarabine in a phase 3 trial with survival as an endpoint. In addition to problems in defining a population of patients who cannot tolerate induction chemotherapy, it has been difficult to prove that the side effects of such treatment are less than what would

be expected with "7 & 3". This was the major problem, as identified in an FDA review, with a phase 2 study of clofarabine, a drug with considerable single agent activity, but with durations of marrow aplasia similar to what occurs after standard induction chemotherapy.
It seems likely that the limits of the benefit from chemotherapy have been defined, given the multiple mechanisms of resistance inherent in the stem cell origin of this group of leukemias. Real progress will be difficult but may depend on novel immunologic approaches and hopefully better understanding of stem cell biology. Until better science prevails, this complex decision in older patients is a reminder that there is still an "art" to medicine and consultations with experienced leukemia centers are advisable.

SP-014
CURRENT TREATMENT OF PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS (MPN)

Petro E. Petrides. *Referral Center for MyeloProliferative Neoplasms at Hematology Oncology Center, Munich, and Ludwig Maximilians University Munich, Department of Medicine, Germany*

Treatment of patients with MPN (primary thrombocythemia, polycythemia vera and myelofibrosis) starts with the education of the patient about the nature of these diseases (signs and symptoms, risk of thrombosis and bleeding, risk of transformation into fibrosis or leukemia) and how changes of life styles (avoiding of smoking, physical exercise, weight control, use of compressing stockings, mediterrenean diet) can contribute to a prevention of disease associated complications.
The therapeutic strategy ranges from a „wait and watch" approach (in low risk thrombocythemia) to stem cell transplantation (in high risk myelofibrosis).
Initial therapeutical step is the use of an antiantiaggregating agent such as aspirin depending also upon the platelet count since elevations of platelets cause secondary von Willebrand factor deficiency increasing the bleeding risk.
In polycythemia vera, phlebotomy is the treatment of choice. If cytoreductive treatment is indicated hydroxyurea (for over 40 years), anagrelide (for 20 years) and interferon-alpha are available. Hydroxyurea is easy to handle, inexpensive and usually well tolerated but can cause skin problems in sun exposed areas and leukemia upon long term use in some susceptible individuals. Anagrelide selectively lowers platelet counts and is free of any proleukemic activity. Interferon-alpha had been shown some 20 years ago to be effective but lost its attractivity because of too many side effects. Nowadays, however, the situation is changing since pegylated interferon-alpha preparations are being introduced which are much better tolerable. In the same vein, slow release forms of anagrelide even further increase its therapeutical potential. For patients with myelofibrosis the JAK2 inhibitor ruxolitinib has shown to prove the principle of a targeted therapy. Ruxolitinib alleviates symptoms of myelofibrosis patients but is palliative in nature since the course of the disease (in contrast to the effects of tyrosine kinase inhibitors in chronic myeloid leukemia) is not altered. Only stem cell transplantation is curative for a small cohort of patients who are fit for this therapy.
Taken together, all the therapeutic options discussed represent a continuum of developments which will lead in the future to further improved options of therapy.

SP-016
INVESTIGATIONAL APPROACHES TO TREATMENT OF *BCR-ABL*1-NEGATIVE MPNS

Tariq I. Mughal**.** *Tufts University Medical Center, Boston, MA 02111*

Following the seminal description of the tyrosine kinase, JAK2, being involved in the JAK/STAT pathway and causally associated in the pathogeneisis of the *BCR-ABL*1-negative myeloproliferative neoplasms (MPNs) a decade ago, many efforts have assessed the role of targeted therapies in various MPNs, in particular ruxolitinib, a type I JAK1/2 inhibitor, which bind the active conformation of JAK2, telomerase inhibitors and alpha interferons. Current experience with ruxolitinib, which is currently the only licensed JAK inhibitor for patients with high risk mylofibrosis (MF) and hydroxyurea resistant/refractory polycythemia vera (PV), suggests a qualified clinical response, with the notable lack of a major effect on *JAK2* mutant allele. Numerous clinical trials with type I JAK inhibitors and also other novel agents, as monotherapy or in combination are now in progress. Two monotherapy phase 3 trials (PERSIST-1 and -2) assessing the JAK2/FLT3 inhibitor pacritinib (SB1518) have now been completed, and the initial results from PERSIST-1 demonstrate impressive efficacy and safety. Pacritinib decreased MF-related symptoms and spleen volume in 41% and 25% of evaluable patients, respectively, including those with significant baseline thrombocytopenia (<50,000/μl). The drug does not appear to have a significant negative impact on hemoglobin or platelet count and the most relevant side effect of note, so far, is grade 3 diarrhea, which occurred in <5% of the study cohort. Another JAK2 inhibitor, momelotinib (CYT387) has demonstrated significant activity in MF patients with a favorable impact on disease-associated anemia, though peripheral neuropathy has been observed; two randomized phase 3 trials are ongoing, including a randomized comparison with ruxolitinib in newly diagnosed patients. Other candidate approaches include HSP90 inhibitors, anti-fibrotic agents such as PRM-151, pan-histone deacetylase inhibitors such as panobinostat, PI3-kinase inhibitors such as BKM-120, hedgehog pathway SMO inhibitors such as LDE225 and PF04449913, and a telomerase inhibitor, imetelstat, alone or in combination with type I JAK2 kinase inhibitors. Interim data suggest qualified responses similar to those seen with ruxolitinib monotherapy, though with minimal worsening of anemia or thrombocytopenia. Activity of alpha interferon in *CALR*-mutant MPN, in contrast reveals molecular remissions, though no complete molecular responses. Early experience with a JAK1 inhibitor, INCB039110, as monotherapy in MF patients also demonstrates an improvement in MF-associated symptoms and splenomegaly, but in contrast to ruxolitinib, with minimal cytopenias. Last, but not least, in an attempt to improve inhibition of JAK2 activation, efforts are assessing the role of type II JAK inhibitors, such as NVP-CHZ868, which inhibit JAK2 in the inactive conformation.

SP-017
TARGETING CD30 IN HEMATOLOGICAL MALIGNANCIES

Hanan Hamed. *Professor of Internal Medicine and Clinical Hematology, Ain Shams university, Cairo – Egypt*

CD30 is a transmembrane glycoprotein with a molecular weight of 120 kDa [1]. It is a member of the tumor necrosis factor receptor (TNFR) superfamily, which is likely to be crucial for regulating proliferation and differentiation of lymphocytes [2]. CD30 has limited expression in healthy tissue or on resting lymphocytes which makes it an excellent therapeutic target [3]. In nonpathologic conditions, CD30 expression is generally restricted to activated B and T lymphocytes and NK cells, with lower levels in activated monocytes and eosinophils. In addition, CD30 is

found on a small percentage of CD8-positive T cells [4]. Classical Hodgkin lymphoma (HL) relapses after or is refractory to upfront multiagent chemotherapy in 20%–30% of patients. Brentuximab vedotin (BV), an anti-CD30 antibody– drug conjugate, has demonstrated significant activity and manageable toxicities in advanced HL [5]. Brentuximab vedotin (SGN-35) is a CD30-directed antibody-drug conjugate (ADC), which can induce cell-cycle arrest and apoptosis, with proven efficacy in patients with CD30-positive malignancies, including Hodgkin lymphoma (HL), peripheral T-cell lymphoma, diffuse large B-cell lymphoma, and systemic anaplastic large-cell lymphoma (SALCL) [6]. All these data will be briefly discussed in the presentation

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SP-018

FIRST LINE THERAPY FOR MULTIPLE MYELOMA

Evangelos Terpos. *Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece*

Therapy options for newly diagnosed MM (NDMM) focus on disrupting myeloma cell-bone marrow stroma interactions, enhancing the immune system response, and specific targeting of myeloma clonal cells. Proteasome inhibitors (PI) have become an integral part of therapy regimens for MM. The combination of the first generation PI, bortezomib and dexamethasone (VD) or bortezomib/thalidomide/dexamethasone (VTD) for use as induction therapy for adult patients with NDMM who are eligible for high-dose chemotherapy with autologous stem cell transplant (ASCT) was approved by the European Commission in 2013. The recommendation to use a bortezomib-based regimen is based on the results of randomized trials, which have been summarized in two meta-analyses and which confirmed the superiority of bortezomib-based regimens over conventional regimens. Sonneveld et al. could show that bortezomib-based induction (PAD) was significantly superior versus non-bortezomib-based induction (VAD) in terms of post-transplantation CR+nCR rates (38% vs 24%, P<0.001), median PFS (35.9 vs 28.6 months, P<0.001) and 3-year OS rates (79.7% vs 74.7%, P=0.04). Despite a lack of regulatory approval, the use of post-transplant therapy, in particular consolidation, defined as a short distinct course of treatment, is increasing across Europe in routine practice, with VTD being the predominant regimen used. Bortezomib has also been investigated in the maintenance setting, resulting in significant improvements in PFS; however, in these trials bortezomib was also used during induction therapy. Hence, it is as yet not clear which part of bortezomib exposure contributed to the results. Subcutaneous dosing of bortezomib in MM has been demonstrated to be as active as intravenous dosing with a better toxicity profile in NDMM. Furthermore the combination of bortezomib with melphalan and prednisone (VMP) is considered one of the standards of care for NDMM patients who are not eligible for ASCT. The second generation PI, carfilzomib, has also been tested in NDMM but has not been approved yet for this indication. The combination of carfilzomib, lenalidomide and dexamethasone (KRD) followed by lenalidomide maintenance provides high rates of deep remission and minimal residual disease (MRD) negativity. The combination of KRD with clarithromycinin NDMM was also reported to be safe and active with ORR of 91.7% and very good partial response (VGPR) of ~55.6%, which included a majority of patients with high-risk cytogenetics. As an induction therapy, carfilzomib with cyclophosphamide and dexamethasone (KCD) in transplant eligible NDMM was well tolerated with response rates of 87% and VGPR of ~48% after 4-6 cycles. The novel PI ixazomib, used in an oral regimen with lenalidomide, has been reported to provide response rates of 23-33% in young and elderly patients with NDMM. Following induction with ixazomib/lenalidomide/dexamethasone, maintenance of up to 1.5 years with ixazomib alone improved response rates with a median duration of response of 26.5 months in NDMM patients not undergoing SCT. Clinical studies assessing single agent ixazomib maintenance after auto-SCT and in combination with lenalidomide after auto-SCT are ongoing.

The IMiDs, thalidomide, lenalidomide and now pomalidomide, have changed the landscape in the management of myeloma patients. The combinations of melphalan, prednisone and thalidomide (MPT) and of cyclophosphamide, dexamethasone and thalidomide (CDT) are widely used for NDMM patients who are not eligible for ASCT. The results of the phase III FIRST study showed that continuous Rd is very effective for NDMM patients who are not eligible for ASCT. Compared to MPT, Rd prolonged both PFS (median: 25.5 vs. 21.2 months) and OS (median: 59 vs. 48.5 months). FDA approved Rd for NDMM on the 18th of February 2015. Maintenance therapy with IMiDs has been also investigated in a number of trials in the post-ASCT setting. Of note, none of the available agents is approved for use in maintenance. With thalidomide, the treatment duration is limited by toxicity concerns, in particular peripheral neuropathy (PN), however, if tolerated it can be considered. Interestingly, in patients with adverse risk cytogenetics, thalidomide maintenance was shown to result in shorter OS and should therefore not be used in the presence of these characteristics. Lenalidomide maintenance has been investigated in three randomized trials, all of which demonstrated a PFS benefit with the agent, while OS was improved in two of the studies. In the first studies investigating the long-term administration of lenalidomide, an increased risk of second primary malignancies (SPM) was observed, which has been carefully analyzed in different studies in the front-line and relapse settings. It has been demonstrated that the increased risk of developing SPMs is related to melphalan exposure, being more pronounced with the oral administration of melphalan, as well as to advanced age. Of note, the use of lenalidomide plus steroids does not appear to increase the risk of SPM. On the whole, the benefit in prolonged PFS and OS gained with lenalidomide maintenance appears to outweigh the risk of developing an SPM.Single agent lenalidomide has also recently been shown to be beneficial to patients with smoldering MM with more than 50% of study participants achieving stable disease at 17 months. Furthermore, in combination with dexamethasone, disease progression was delayed and improvements to OS were observed compared to observation alone.

SP-019

SMOLDERING MULTIPLE MYELOMA: UPDATES ON SMOKE VERSUS FIRE

Hande H. Tuncer. *Lahey Hospital and Medical Center, Department of Hematology-Oncology, Burlington, Massachusetts, USA*

Smoldering multiple myeloma (SMM) is a relatively rare clonal plasma cell disorder which represents a transitional biological phase between monoclonal gammopathy of unknown significance (MGUS) and multiple myeloma. It consists of a heterogeneous population with variable risk of malignant transformation. There have been significant advances in understanding the pathobiology of this entity, yet there is still no single diagnostic tool available to distinguish the subset of patients who have higher risk of progression to myeloma from the ones who clinically behave more like MGUS. On the other hand, there are updated definitions and diagnostic criteria for multiple myeloma by the International Myeloma Working Group (IMWG) which shifted some SMM patients to the multiple myeloma category, affecting the timing of therapy. Furthermore, there is emerging data supporting the benefit of treatment of high risk SMM with improved progression-free and overall survival.

SMM is defined by the presence of a serum monoclonal (M) protein of 3 g/dL or more and/or 10% to 60% clonal plasma cells in bone marrow without evidence of end-organ damage. (MGUS defined as M protein less than 3 g/dL and/or less than 10% clonal plasma cells). Patients who have more than 60% bone marrow plasma cells, serum involved/uninvolved free light chain (FLC) ratio of > 100 or those with 2 or more focal lesions on MRI are now considered to have multiple myeloma rather than SMM.

The risk of progression from SMM to multiple myeloma is around 10%/year for the first five years which steadily decreases and becomes comparable to MGUS after ten years (1% /year). Several clinical and laboratory features have been identified as risk factors of progression; defining the high risk SMM. These include M protein> 3g/dL, decrease in two uninvolved immunoglobulin levels (AKA immunoparesis), IgA type M protein, increased serum free light chain ratio (≥ 8), adverse cytogenetic abnormalities such as 17p deletion, 1q gain, t(4;14), accelerated increase in M protein level (≥25% increase in 6 months), increased bone marrow (>50%) and circulating plasma cells, and abnormal foci in MRI or PET imaging.

Baseline diagnostic studies include complete blood count, serum creatinine and calcium, serum and urine protein electrophoresis with immunofixation, skeletal survey and bone marrow biopsy with fluorescent in situ hybridization studies and flow cytometry. IMWG has published updated diagnostic recommendations earlier this year, emphasizing the role of MRI to identify some high risk SMM patients who now are considered to have myeloma and should be treated as such. MRI is more sensitive than skeletal survey for determining bone involvement and demonstrating early marrow infiltration. 20% to 50% of patients who show no lesions on plain radiographs show abnormal bone marrow on MRI. All SMM patients are now recommended to undergo whole-body or spine-pelvis MRI. If they have >1 focal lesion greater than 5 mm in diameter, the risk of progression is around 70% in 2 years. Therefore, they are considered as active myeloma and should be offered anti-myeloma therapy. If the lesions are small, a follow-up MRI is offered in 3 to 6 months.

The current standard of care for SMM is observation until clinically significant events appear. This recommendation is based on the lack of data showing any benefit from early therapy reported in early studies such as with melphalan, thalidomide and biphosphonates. The design and results of these studies were probably challenged by the difficulty to define the subset of SMM patients who would truly benefit from early intervention. The latest study conducted by PETHEMA group in 2013 comparing observation versus lenalidomide and steroids in high risk SMM patients has brought back more enthusiasm and debate to the topic. In this open label study, over hundred high risk SMM patients were randomized to receive placebo versus lenalidomide and dexamethasone. Patients in the treatment arm had a superior 3-year progression free survival (77% vs 30%; P < 0.001) and overall survival (94% vs 80%; P = 0.03). The study has been criticized for concerns of risk stratification and generalizability, yet it provided propelling data for further studies.

SMM constitutes a biological progression of a clonal disorder resulting an incurable malignancy. Understanding the pathogenesis represents a critical opportunity to explore therapeutic targets that may lead to delay or even prevent progression to overt malignancy.

SP-020

UPDATE ON HAIRY CELL LEUKEMIA

Farhad Ravandi. *Professor of Medicine, Department of Leukemia, University of Texas – MD Anderson Cancer Center*

Progress in the management of patients with hairy cell leukemia (HCL) over the past several decades clearly reflects how success in understanding the biology of leukemogenesis is leading to better and more disease specific strategies. From a disease that could only be inadequately managed by splenectomy in the 1960s, this uncommon leukemia can now be effectively treated with a number of exciting and relatively non-toxic strategies which are extremely well tolerated by the patients and lead to long term survival, if not cure.

The nucleoside analogs, cladribine and pentostatin, were truly revolutionary and produced complete responses in the vast majority of the patients. However, more recent long-term follow-up reports of patients treated with these agents have clearly shown that the progression free survival curves do not plateau and a fair proportion of patients relapse within the first 4 to 5 years of therapy [1]. Since this is a disease of younger patients (as compared with most other lymphoid neoplasms) with a median age at diagnosis in the 50s, we need to do better than monotherapy with the nucleoside analogs at least in those who are destined to relapse. Clearly, the best strategy would be to identify the subgroup of the patients who is most likely to relapse after therapy with cladribine and pentostatin and several recent reports have suggested that this may be possible. For example, patients with unmutated immunoglobulin heavy chain variable region gene (*IGHV*) and those with the VH4-34 variety have been identified to be at high risk of failure after therapy with cladribine [2,3]. Similarly, patients with variant form of HCL have been known to be less response to single agent cladribine or pentostatin.

Development of monoclonal antibodies such as rituximab has truly improved the outcome of patients with lymphoid neoplasms including follicular and large cell lymphoma and chronic lymphocytic leukemia. A number of studies have demonstrated that their inclusion to the established cytotoxic chemotherapy regimens lead to significant improvements in progression free and overall survival. We and others have reported that this is also true for patients with HCL where addition of 8 weekly doses of rituximab to cladribine or pentostatin appears to be effective in reducing the chance or relapse [4], although this is yet to be demonstrated in large randomized trials, likely due to the rarity of the disease.

Further advances in understanding the biology of HCL, most importantly, the identification of the almost universal occurrence of the *BRAF* V600E mutation in this disease [5] and development of novel agents such as BRAF inhibitors, B-cell receptor inhibitors, as well as novel immune based therapies such as the potent immunotoxin moxetumomab pasudotox and newer CD20 directed monoclonal antibodies is likely to further broaden our armamentarium for the effective treatment of HCL. It is likely that universal cure in this disease will soon be a reality.

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SP-021

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): CURRENT AND FUTURE TREATMENT STRATEGIES

Carmino Antonio De Souza. *Hematology and Blood Transfusion Center – University of Campinas-SP – Brazil*

DLBCL is the most common type of NHL. Occurs in 30-40% of new diagnoses and presents heterogeneous clinical and morphological features. The cure rate ranges from 80-85% for patients with limited disease to about of 40-50% for advanced disease. IPI score and age adjusted IPI (aaIPI) remain as benchmarks of DLBCL prognosis. DLBCL could be divided in three major subgroups of prognosis: elderly pts (>60 years, aaIPI=0-1); young pts with low risk (<60 years, aaIPI=0-1) and, young pts with high risk (aaIPI=2-3). Bulky disease [1] and cytomorphology of bone marrow involvement seem to be related to bad prognosis in DLBCL [2]. The standard therapy is the anti CD-20 monoclonal antibody and "CHOP" or "CHOP like" chemotherapy every 14-21 days for six cycles. The current challenges in DLBCL are: molecular classification and its prognostic impact; upfront therapy for high risk pts; the role of CNS prophylaxis; salvage treatment and; new treatment strategies. In 2002, Rosenwald et al published the use of molecular profiling to predict survival after chemotherapy in DLBCL [3] and demonstrated better survival for the Germinal-Center B Cell-like comparing to activated-B-Cell-like and type 3. In 2012, Visco et al confirmed better outcome of GCB type over ABC and non-GCB types [4]. Confirmation of the molecular classification and outcome can be obtained by immunohistochemistry [5]. The presence of molecular biomarkers (Bcl2, Bcl6, *MYC* rearrangements) have poor independent prognosis. "Double" hits or "triple" hits present inferior survival particularly in GCB subtype [6,7]. Concerning therapies, Cunningham et al in a phase 3 study did not show any difference in outcome using R-CHOP-14 and R-CHOP-21 [8]. The German high-grade lymphoma study group (DSHNHL), in a phase 3 trial for high-risk DLBCL pts, showed better outcome for high-dose chemotherapy (CT) (Mega-CHOEP) compared to conventional CT (CHOEP-14). However, grades 3-4 non hematological adverse events were higher among pts in the intensified arm [9]. Wilson et al in a multicenter study using dose-adjusted-EPOCH-rituximab showed good results in GCB and low-level Ki67 (<60%) non-GCB sub sets. However, pts in the non-GCB group presenting Ki67>60% still presenting poor outcome [10]. The role of CNS prophylaxis still remains controversial. Pts with CNS relapse presenting poor prognosis (OS = 2-5 months). High-risk pts and/or presenting "special" sites (testis, sinus, orbit, epidural, breast and kidney) are the main target for CNS prophylaxis. Siegal et al suggested an algorithm for therapy and prophylaxis [11]. The salvage therapy for refractory or relapsed DLBCL includes immune-chemotherapies, autologous stem cell transplantation (ASCT) and allogeneic stem cell transplantation. Philip in the 90th, in a randomized trial, showed the superiority of ASCT over DHAP conventional CT [12]. Several other randomized trials, also in the Rituximab era, confirmed these data using other conventional R-CT (R-ICE, R-DHAP, R-ESHAP, R-GDP). The French group demonstrated better outcome with ASCT as salvage treatment in GCB-type [13]. The new therapeutic strategies include drugs acting in microenvironment, cell cycle, PI3K/AKT/mTOR, B-cell receptor, proteasome, cell death (apoptosis) and, protein deacetylases.

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SP-022

MANTLE CELL LYMPHOMA

Khalid Halahleh. *Palestine-Jerusalem*

Mantle cell lymphoma (MCL) is a mature B-cell neoplasm defined as a distinct entity in the early 1990. Is MCL characterized by the presence of specific translocation t(11,14), that regulates the expression of Cyclin D1 in almost every patient. Within this entity, there is a clinical and biological heterogeneity-some patients present with an indolent course and others present with a more aggressive disease course-blastoid variant. In the last few years, we got an insite on the clinical and biological subtypes of MCL with typical phenotype (CD5+, CD23 -, and Cycline D +), which

can be supplanted by conventional and FISH studies to detect the specific translocation.

MCL represents 6-7% of all NHL. Patients with MCL have a median age of 60s and have a striking male predominance. Cases with MCL can be risk stratified by using of MIPI which includes PS, age, LDH and WBC and Ki-67 in the modified version. Accordingly patients can be divided to low risk, Intermediate and high risk groups with different OS and PFS.

My approach in the treatment of patients with MCL is to differentiate younger <65 year fit patients from older patients with comorbidities and poor PS and weather they are symptomatic or not. Younger fit patients will be treated with a combination of chemoimmunotherapy especially R-CHOP alternating with R-DHAP based on a phase III EMCL network data showing the importance of high dose ARA-C and the achievement of deep remission before going into consolidative autologous stem cell transplantation. Elderly and poor PS patient can be treated with immunochemotherapy modified or simple immunotherapy without consolidation by ABMT. Of course asymptomatic patients can be watched. With the aforementioned approach, MCL seems incurable and we need to include in the treatment of MCL novel therapies working on the functional pathways of pathogenesis of the disease including Proteasome inhibitors, the PI3Kinase inhibitor(GS-1101, Idelalisib),mTOR pathway-Temserulimous, immunomodulatory agent lenalidomide and more recently, brutons tyrosine kinase (BTK) inhibitor (Ibruitinib) and an allogeneic stem cell transplant as there is a high evidence of graft versus lymphoma effect in relapsed setting.

In my presentation, I will discuss the options of treatment of MCL, especially the incorporation of novel agents and there benefits.

SP-023
INDOLENT LYPHOMAS: PRACTICAL CLINICAL APPROACH

Berksoy Sahin. *Cukurova University Medical Oncology Department*

Management of the patients with indolent lymphoma is a state of art. Although there is some common approach for the management of these patients, follicular (22%), marginal zone (6%), and lymphoplasmacytoid lymphomas(3%) are distinct B-cell lymphoid neoplasia. On the other hand, mycosis fungoides, is a T-cell lymphoid neoplasia with its unique clinical presentation and management. Small lymphocytic lymphoma(6%) is an other entity that will be mentioned in other topic (CLL by an other author) in this journal.

Follicular NHL (FL): Before treating a patient with FL, grading (I, II, III), staging (Ann-Arbor), prognostification systems (FLIPI) and symptoms should be evaluated.

In patients with early stage FL grade I-II, involved-site radiotherapy (ISRT; 24–30 Gy) is the preferred treatment (MS: 14 years, 15yS: 40%, 15yRFS: 40%) but observation (if toxicity a problem), and immunochemotherapy are alternate options. The treatment in patients with advanced stage FL Grade I-II, should be individualized according to GELF criteria (symptoms, cytopenia, bulky disease, progression rate) and patients conditions (age, comorbids, goal of therapy). Older (>70 y) and asymptomatic patients should be observed. Locally bulky and symptomatic (if unable to tolerate systemic treatment) patients can be treated with ISRT ±systemic therapy. Single-agent rituximab (CD20 antibody) is the preferred first-line therapy for elderly or infirm patients. For firm symptomatic patients, adding rituximab to chemotherapy provided benefits over giving that same chemotherapy alone (PFS: 70-80% vs 40-65% and OS: 85-95% vs 75-80%). Bendamustine or CHOP are the preferred chemo backbones with respect to fludarabine containing regimens (stem cell toxicity, secondary malignancy). Maintenance treatment is recommended for patients responded to 1L chemoimmunotherapy. For the relapsed patients, (excluded for transformation; biopsy for SUV>13.1 at PET), radioimmunotherapy (RIT) or chemoimmunotherapy regimens used in 1L treatment (BVR, FCM-R,) can be recommended. Idelalisib is approved for patients who received at least 2 prior regimens.

Marginal zone lymphoma (MZL): Three distinct subtypes of MZLs exist, MALT (mucosa-associated lymphoid tissue), splenic, and nodular. Fort the early staged patients with Gastric MALT (H.pylori- and t(11;18)+ or antibiotic refractory disease), ISRT is the preferred treatment but rituximab may be an option also. The treatment for patients with stage III-IV is similar to advanced stage FL treatment. Gastrectomy is generally limited to specific clinical situations such as life-threatening hemorrhage. Patients with Non-gastric MALT Lymphomas is treated with ISRT at stg I-II, and with systemic chemoimmunotherapy at stg III-IV. MALT lymphomas coexistent with large-cell lymphoma should be managed according to the recommendations for DLBCL. Splenic MZL; symptomatic patients should be treated with splenectomy or rituximab and antiviral therapy added for HCV+ patients. Patients with Nodal MZL are treated in a similar fashion to FL.

Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma: The treatment should only be initiated for patients with symptoms. (hyperviscosity,neuropathy,organomegaly;amyloidosis,cryoglobulinemia; cold agglutinin disease, cytopenia). In symptomatic hyperviscosity, initial plasmapheresis is recommended. Rituximab alone or with combination (R-CD; CP-R; CHOP-R, bortezomib, thalidomide, bendamustine) forms backbone for primary systemic treatment and can be recommended in patients with a good response to prior rituximab.

SP-024
MANAGEMENT OF SICKLE CELL DISEASE

Salam Alkindi. *Sultan Qaboos University, Muscat-Oman*

Sickle cell disease (SCD) is a common inherited disorder characterized by a single-point mutation (replacement of glutamic acid with valine in the position 6) of the β-globin subunit of hemoglobin (Hb) resulting in the formation of the Hb sickle (HbS) variant. This result in the formation of crescent -shaped sickled red cells that lead to occlusion of the microvascular circulation, leading to infarction, and chronic hemolytic anemia. As a consequence, there is constant liberation of free Hb as well as constant injury of vessels that contains them, leading to inflammation, platelet activation, increased adhesion of RBCs to the vascular endothelium, and abnormal nitric oxide metabolism. These patients present with what is known as vaso-occlusion (VOC) crisis resulting in severe pain, but these VOCs can occurs in other organs leading to acute manifestations such as acute chest syndrome, stroke and also sequestration crisis in liver & spleen (pooling). Repeated episodes of injury can result in chronic end-organ manifestations such as pulmonary hypertension, hepatic and cardiac dysfunction. The management of patients with SCD relies on better understanding of the pathophysiology of the disease and aiming at overcoming these interacting pathways. Since this disease is a hemolytic disease, blood transfusions plays an important role in its management, both at the acute setting (given as top-up or exchange transfusions) for the management of ACS, acute sequestration or stroke, or in the chronic setting when given for the primary or secondary prevention of stroke, recurrent ACS or severe painfully crisis. However blood transfusions are not without price and that includes allo-immunization, infection risk and iron overload. Hydroxyurea is the only drug that is known to reduce VOCs, hospitalization, transfusion needs, end-organ damage (including stroke and ACS) and mortality. It's licensed for both adults and children and with established safety and efficacy record. Hematopoietic stem cell transplant (HSCT) remains the only curative management for this disease. It remains restricted for various reason including availability of suitable donor, accessibility to patients who need it most, and convection of treating physicians about its role (fear of end-organ complications including rejection and graft versus host disease). However the option of HSCT is expanding particularly with close to 90% DFS and expanding

options for donors including, cord blood, hap-identical and unrelated donor transplants. SCD is a complex disease, with many interacting facets into its pathophysiology, invites for better understanding of the disease, which is a key for success in designing novel therapies including gene therapy and other supporting therapy. Also this disease requires multi-disciplinary approach (including comprehensive management programs delivered at day care level) and incorporating neonatal screening and other preventative elements.

SP-026

THROMBOPHILIA SCREENING IN 2015: WHICH PATIENTS AND WHICH TESTS?

T. Pierre. *Hematology Department, Pasteur University Hospital, Nice, France*

Venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism, is a multifactorial disease with genetic and environmental factors that interact. Acquired environmental factors are more common than inherited thrombophilia, and recent trauma, surgery, prolonged bed resting, plaster cast, cancer, inflammation, advanced age, pregnancy, estrogen therapy, and advance age, are considered as risk factor for VTE. In the mid-19th century, Virchow identified hypercoagulability as part of the triad leading to venous thrombosis, but the specific causes of hypercoagulability remained a mystery for a century, with antithrombin III (AT) deficiency being the first specific cause to be identified in the mid-seventies. Since then, many other causes of thrombophilia, both hereditary and acquired, have been discovered. Among hereditary abnormalities, deficiency in natural anticoagulants AT, protein C and S, and common single nucleotide polymorphisms (SNPs) i.e. Leiden mutation of factor V and G20210A mutation of prothrombin genes are well documented. Deficiencies of antithrombin, protein C, and protein S increases the risk of a first VTE by at least 10-fold, but they are rare (<0.5%) in the general population, whereas FV Leiden and the prothrombin G20210A gene mutations, which increase this risk by 2-5-fold are more common (2-5%) but only in the Caucasian population. High levels of coagulation FVIII, FIX and FXI, were also reported to be associated with increased risk of VTE. The most common acquired cause is the presence of lupus anticoagulant and/or high titer of antiphospholipid antibodies. Although controversial, screening for thrombophilia has become common. Currently, it is being used in a frequency and to an extent which is not supported by evidence. In order to protect patients from unnecessary worry and stigmatization, but also for reasons of cost effectiveness, thrombophilia testing should be reduced to a very small number of medically justifiable indications. These issues will be discussed.

SP-027

INVASIVE FUNGAL DISEASE MANAGEMENT IN HAEMATO-ONCOLOGY

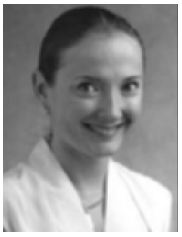
S.G. Agrawal. *Department of Haemato-Oncology, St Bartholomew's Hospital, Barts Health NHS Trust, London; Pathology Group, Blizard Institute, Queen Mary University of London*

Antimicrobial stewardship has become a headline priority for governments and for international bodies, such as WHO. Antifungal stewardship is a highly specialized subset of this approach. I will discuss stewardship in the context of Haemato-Oncology as a further tool to ensure optimal patient management and resource utilization, over and beyond the development of care pathways for invasive fungal disease (IFD). A successful pathway requires "ownership" of the pathway by the clinical team looking after the patient, radiology, microbiology, infectious disease and respiratory physicians…My presentation will focus on the current debate on management strategies for IFD in Haemato-Oncology and the changes in our management algorithms over the last 15 years at St Bartholomew's Hospital, London. I will present our updated diagnostic strategy, which uses three tests directed at *Aspergillus* detection – PCR, galactomannan and the LFD assay. The introduction of this triple testing strategy – "TRIADx" – will support the antifungal stewardship team, which will work closely with the Haemato-Oncology physicians and guide all aspects of IFD management.

SP-030

CANCER STEM CELL BIOLOGY: TUMOR-ASSOCIATED MACROPHAGES DRIVE THE EPITHELIAL-TO-MESENCHYMAL TRANSITION IN METASTATIC CANCER

Vera S. Donnenberg[1,2,3], Jayce Jieming Zhang[1,4], Vincent Riccelli[1,2], Noah S. Donnenberg[1,6], David J McFall[1,7], E. Michael Meyer[1], Albert D. Donnenberg[1,8,9]. *[1]University of Pittsburgh Cancer Center, Hillman Cancer Center, Pittsburgh, Pennsylvania, USA; [2]McGowan Institute of Regenerative Medicine; [3]University of Pittsburgh School of Medicine, Dept. of Cardiothoracic Surgery; [4]Xiangya School of Medicine, Central South University, Changsha City, China; [5]University of Norte Dame; [6]Central Catholic High School, Pittsburgh, PA; [7]Princeton University; [8]Department of Hematology-Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [9]University of Pittsburgh School of Medicine, Dept. of Medicine*



Primary and metastatic breast cancers are different entities with different biologies. One of the major clues concerning the nature of the transition from occult primary disease to aggressive metastatic disease is the epithelial to mesenchymal transition (EMT), a phenotypic change in which epithelial cancer cells lose epithelial characteristics and take on the properties of mesenchymal stromal cells, including the ability to detach, invade and disseminate . By the mesenchymal to epithelial transition (MET), mesenchymal-like tumor cells, which have seeded distantly, can revert to an epithelial phenotype, wholly or in part, and cooperate with the local perivascular niche to generate a vascular supply (angiogenic switch). All of these events contribute to the formation of new micrometastatic colonies of tumor cells. Human tumors are complex and heterogeneous: epithelial, mesenchymal, stromal and perivascular-endothelial and immune cells can be observed in both metastatic lesions and primary tumors [1-4]. EMT also endows cancer cells with stem cell-like traits, including increased resistance to various therapies and expression of key stem cell-associated markers such as CD90 and CD44 [2,3,5] and invasion specific markers. We and others have shown that CD90 is a key molecule present on cancer stem cells with high invasive potential [2,3] as well as on tumor supporting stroma. It is also present on normal perivascular cells [6,7] responsible for microvasculature generation. We have also shown that tumor stem-like EMT cells, physically located at the invasive front of primary cancer [3], have been linked to tumor metastasis . Further, we demonstrated that these cells interact with tumor-associated macrophages (TAM) to create a CSC-niche, amplify EMT and promote an invasive tumor type [2]. Using cell culture and xenograft models we have shown that EMT is initiated by CD90-CD11b binding and EphA4-EphA4 receptor binding, mediating direct physical interactions between tumor-associated macrophages (TAM) and tumor cells . Macrophage adhesion and interaction with CD90+ cancer stem cells results in NF-κB-driven expression and secretion of a cohort of cytokines by the tumor cells, especially IL6, IL8 and GM-CSF, polarizing the tumor cells to an invasive, EMT phenotype. A similar interaction occurs with CD90+ pericytes and endothelial progenitor cells and tissue resident macrophages, resulting in the secretion of vasculogenic chemokines and localized promotion of de novo angiogenesis. Currently we have shown that TAMs are rare but present in primary tumors, and are exclusively of M2 polarization as determined by the absence of HLA-DR and expression of CD163; that TAM

associate with CD90+ CD44+ tumor cells and that this association drives the epithelial to mesenchymal conversion of patient-derived tumor cells *in vitro* and in an *in vivo* xenograft model. Metastatic tumors often contain dramatic proportions (mean = 30%) of macrophages, some of which simultaneously express both M1 and M2 associated markers.

Taken together, tumor/stroma interactions within the perivascular niche foster both: 1) TAM/tumor juxtacrine interaction promoting EMT and 2) TAM-pericyte/endothelial progenitor interactions promoting angiogenesis. Interventions to interrupt this 3-way crosstalk should be incorporated into therapies directed at preventing the progression to metastatic disease [8].

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SP-032
ENGINEERED T-CELL TREATMENT IN THE AREA OF ACUTE LYMPHOBLASTIC LEUKEMIA

Francesco Saglio. *Pediatric Onco-Hematology, Stem Cell Transplantation and Cellular Therapy Division, A.O.U. Citta' della Salute e della Scienza di Torino, Ospedale Infantile Regina Margherita, Torino, Italy*

Acute Lymphoblastic Leukemia (ALL) is a disease characterized by an abnormal proliferation of either B or T-cells progenitors. Although the prognosis of patients affect by ALL has dramatically improved in the past decades thanks to the introduction of combination chemotherapy, the development of molecular targeted drugs (i.e. tyrosine kinases inhibitors) and the application of hematopoietic stem cell transplantation in selected cases, there is still a significant proportion of patients for which consolidated therapies are ineffective.

The general role of T cells in controlling ALL by a graft versus leukemia (GvL) effect has long been established by large studies focused on hematopoietic stem cells transplantation and donor lymphocytes infusions, however, graft versus host disease (GvHD) still remains an issue, suggesting that a more specific populations of T cells is needed to enhance the GVL effect and to reduce the complications related to their use.

There are mainly two strategies to manufacture ALL specific T cells: *ex-vivo* expansion and genetic modification.

Ex-vivo expanded T cells are generated by stimulating peripheral blood mononuclear cells with antigen presenting cells pulsed with pool of overlapping peptides spanning the entire sequence of leukemia associated antigens. This technique has some advantages as the ability to generate a product that targets multiple antigens, but at the same time some important limitations as the low affinity of some ALL associated antigens and the dependence of all the process from the HLA-system integrity.

The genetic modification of T cells mainly consists in re-directing T cells specificity either by optimizing high affinity T-cell receptors or by introducing chimeric antigen receptors (CAR) in them.

In this case ALL can be considered an ideal setting for the application of this strategy in consideration of the presence on ALL cells of specific target as CD19.

Each method has its peculiar advantages and limitations, but there is a lack of evidences showing the superiority of one method over the others in pre-clinical studies.

The results of the first clinical trials aimed to investigate the safety and the efficacy of ALL-specific T- cells are promising but still limited to small cohort of patients and only available in very few centers. Future efforts are mainly aimed in improving the safety, the efficacy and the persistence of T-cells *in vivo* while decreasing manufacturing time and conferring protection against immune escape.

SP-033
CLINICAL FINDINGS AND DIAGNOSIS OF FANCONI ANEMIA

Sule Unal. *Hacettepe University, Center for Inherited Bone Marrow Failure Syndromes*

Fanconi anemia (FA) is primarily inherited as an autosomal recessive disorder except for about 2% of the X-linked recessively inherited form. Fanconi anemia is not only a disorder of physical abnormalities and bone marrow failure, but also is characterized with propensity to leukemia and squamous cell carcinoma, in addition to endocrine abnormalities.

The carrier frequency of FA is estimated to be 1 in 300 and recently revised to be 1 in 181 for North America. However the carrier frequency is much higher in certain populations with founder effects for certain genotypes.

The patients with FA are prone to DNA-cross linking agents and the FA pathway involves at least 17 genes that are involved in the repair of DNA injury.

The most common birth defects noted in patients with FA include skin hyperpigmentation/hypopigmentation, café au lait spots, short stature, thumb and radius abnormalities, microcephaly, micophtalmia, kidney abnormalities and ear defects. However at least 25% of FA patients have no appearant physical abnormalities suggestive for FA.

Patients with FA may present with cytopenias, aplastic anemia, myelodysplastic syndrome, leukemia, macrocytosis without any other explanation. Additionally the patients are at risk for head, neck, esophageal and gynecological squamous cell carcinomas. The role of human papilloma virus infection as a risk factor for these tumors is arguable. The patients who are extremely sensitive to chemotherapy and/or radiotherapy should also be considered for diagnostic evaluation for FA. There are several genotype/phenotype correlations in FA patients. Null mutations usually lead to a more severe phenotype compared to hypomorphic mutations. On the other hand patients with FANCD1/BRCA2 and FANCN/PALB2 have more severe birth defects and more pronunced risk for AML development. Whereas the patients with FANCD1/BRCA2 genotype have prominently increased risk for brain and Wilms tumors

development. On the other hand, the patients with c67delG mutation in FANCC have been reported to have less severe birth defects and the later onset of bone marrow failure. ALmost 98% of the patients with FA develop bone marrow failure before 40 years of age and the patients with more severe physical abnormalities have been reported to develop bone marrow failure at an earlier age.

There are various diagnostic modalities used fort he accurate diagnosis of FA. Of these tests, chromosomal breakage (fragility) test is often the first test ordered and the test relies on the types and rates of breakages and rearrangements after challenge with DNA cross-linking agents such as mitomycin C (MMC) and diepoxybutane (DEB). However there are several disorders causing chromosomal instability such as Nijmegen breakage syndrome and other tests might be required in order to confirm the diagnosis. Other diagnostic methods include complementation analysis, next generation sequencing and retroviral complementation analysis.

SP-034

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN FANCONI ANEMIA

Fatma Visal Okur. *Department of Pediatrics, Pediatric Hematology/BMT Unit, Hacettepe University Faculty of Medicine Ankara, Turkey*

Fanconi anemia (FA) is a genetically and phenotypically heterogeneous autosomal recessive disorder characterized by congenital malformations, genetic predisposition to malignancy and progressive bone marrow failure. Although more sensitive and specific diagnostic tests for FA including cytogenetic and molecular diagnostics revealed the presence of FA patients with absence of congenital abnormalities (25-40%) and/or aplastic anemia, all FA patients have a significant risk for the development of MDS/AML and a predisposition towards various forms of solid tumor. Hematological abnormalities usually develop at a median age of 7 years. The risks for the development of bone marrow failure, MDS/AML and solid tumors are 90%, 33%, and 28% respectively, by the age of 40 years (Daley R2,3).

Although allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for bone marrow failure in patients with FA, successful allogeneic transplantation is still challenging for a number of reasons. Cells from FA patients exhibit a significant hypersensitivity to DNA interstrand cross-linking agents such as DNA alkylating agents and ionizing radiation because of defective DNA repair mechanisms. Thus standard conditioning regimens confer a high risk of regimen-related toxicities (RRT) and mortality while reduced intensity regimens result in graft failure. Modifications to FA HSCT conditioning regimens together with progress in transplant medicine such as more accurate HLA typing, new graft engineering technologies and better supportive care have improved the prognosis of FA patients undergoing HSCT. In 1984, Gluckman reported the first successful conditioning regimen for FA patients, including low-dose cyclophosphamide and single fraction limited-field irradiation (Daley# 7). This approach led to a significant reduction in RRT and improved survival especially after HLA-matched sibling donor HSCT. Later, incorporation of fludarabine to conditioning regimens enhanced immune suppression and engraftment without increasing toxicity. T cell depletion of allografts reduced the risk and severity of GVHD. However outcomes of FA patients who receive transplants from alternate donors and/or those with advanced MDS/AML are less encouraging, albeit improving (Ayas, JCO, Minnesota). High rates of acute/chronic graft-versus-host disease (GVHD), graft failure and opportunistic infections particularly after alternate donor HSCT remain as major obstacles. At present major focus has been to decrease or eliminate irradiation from conditioning regimens prior to HLA-matched sibling and/or alternate donor HSCT in order to lower the risk of late complications, particularly late malignancies. Bone marrow is still the preferred stem cell source over PBSC because of its lower risk of GVHD. Haploidentical and umbilical cord blood transplantations in FA are under development for patients who lack HLA-matched related or unrelated donors. In addition, in-vitro fertilization and preimplantation genetic diagnosis (IVF-PGD) might be employed as a means for families to have unaffected children. Determination of HLA haplotypes of embryos simultaneously might help to identify potential HLA-matched sibling donors for an already affected child. All these challenges and new developments provide incentive for further improvements for HSCT in FA patients.

SP-035

CONGENITAL DYSERYTHROPOIETIC ANEMIAS (CDAS)

Achille Iolascon. *Professor of Medical Genetics, Department of Molecular Medicine and Medical Biotechnologies University Federico II, Naples (Italy)*

Erythropoiesis is the complex process that involves differentiation of early erythroid progenitors to mature enucleated red cells. Dyserythropoiesis is a derangement along this process and usually it causes a reduced capacity of cell production. Since this process is accompanied by anemia, it causes an increased erythropoietic signal that causes an enhanced presence of bone marrow erythroid cells.

Dyserythropoiesis may represent a physiological condition or an inherited or acquired disease.

All inherited dyserythropoiesis forms have in common bone marrow erythroid abnormality and erythroid hyperplasia appearance. Three classical types of CDAs have been defined on the basis of bone marrow morphology and this working classification is still used in clinical practice. Both CDA I and II are autosomal recessive diseases. The hallmark of CDA I are macrocytic anemia and bone marrow appearance of incompletely divided cells with thin chromatin bridges between pairs of erythroblasts, which may also be seen between two nuclei in a single cell. On the contrary CDA II patients show a marked increase in bi- and multi-nucleated erythroblasts in their bone marrow.

CDA type III is an autosomal dominant disease with giant multi-nucleated erythroblasts in bone marrow and it appears extremely rare. This latter was first reported in 1962 in a large Swedish family accounting for 34 patients. The causative gene, *Kif23*, was mapped on chromosome 15. There are, however, families that fall within the general definition of the CDAs, but do not conform to any of the three classical types. CDA type IV, a CDA II with negative serum tests, sharing similar bone marrow morphology of CDA III (multi-nucleated erythroblasts), was originally listed in the group of the CDA variants. Mutations in erythroid transcription factor genes (*KLF1*, *GATA-1*) have been recently identified as possible causative genes.

The CDA I and II combined prevalence varied widely between European regions, with minimal values of 0.08 cases/ million in Scandinavia and 2.60 cases/million in Italy. CDA II is more frequent than CDA I, with an overall ratio of approximately 3.2, but the ratio also varied between different regions. The estimations reported are most probably below the true prevalence rates, due to failure to make the correct diagnosis and to underreporting.

The gene responsible for CDA I (*CDAN1* gene) was mapped to the long arm of chromosome 15 between 15q15.1q15.3 by homozygosity mapping performed. The *CDAN1* gene was successively cloned with 28 exons spanning 15 Kb and encoding a protein named codanin-1. In unrelated patients of European, Bedouin and Asian origin, different point mutations were detected. Approximately 90% of patients with a bone marrow suggesting CDA I have codanin-1 gene mutations. All these seem to be independent events and up to now no particularly frequent mutations are present in literature data. Interestingly, no homozygotes or compound heterozygotes for null-type mutations have been identified, supporting an earlier notion that codanin-1 may have a unique function and may be essential during development. Codanin-1 is a ubiquitously expressed protein, still not well characterized. It seems to be related to chromosome structure and it must be involved in mitotic process.

Very recently several families *CDAN1* mutation negative allowed for the identification of a new causative gene: C15ORF41, coding for a protein involved in DNA replication and chromatin assembly.

Sequencing analysis of CDA II patients showed a wide spectrum of different mutations in SEC23B gene in either the compound heterozygous or homozygous state. The disease gene encodes the cytoplasmic coat protein (COP)II component SEC23B, involved in the secretory pathway of eukaryotic cells. COPII is a multi-subunit complex which mediates accumulation of secretory cargo, deformation of the membrane and generation of subsequent anterograde transport of correctly folded cargo that bud from the ER towards the Golgi apparatus. The specificity of the CDA II phenotype seems to be determined by tissue-specific expression of SEC23B versus SEC23A during erythroid differentiation.

An attempt to identify a genotype-phenotype relationship demonstrated that patients with compound heterozygosity for a missense and nonsense mutation tended to produce more severe clinical presentations than homozygosity or compound heterozygosity for two missense mutations. Homozygosity or compound heterozygosity for two nonsense mutations was never found, and it was supposed to be lethal. Very recently *Sec23b* deficient mice was generated and it has not apparent anemia phenotype, but die shortly after birth, with degeneration of professional secretory tissues, pancreas as well as salivary glands. These data demonstrate that *Sec23b* deficient humans and mice exhibit disparate phenotypes, apparently restricted to CDA II in humans and a prominent neonatal pancreatic insufficiency in mice.

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SP-036

SHWACHMAN-DIAMOND SYNDROME: CLINICAL FEATURES AND MOLECULAR PATHOGENESIS

Kasiani C. Myers[1], Audrey Anna Bolyard[2], Jamie Leung[2], Joan Moore[1], Sara Loveless[1], Leann Mount[1], Richard E. Harris[1], Stella M. Davies[1], Sioban Keel[3], David C. Dale[2], Akiko Shimamura[4,5,6]. *[1]Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]Dept of Medicine, University of Washington; [3]Dept of Medicine, Division of Hematology, University of Washington, Seattle, WA; [4]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; [5]Seattle Children's Hospital, Seattle, WA; [6]Pediatrics, University of Washington, Seattle, WA*

Shwachman-Diamond syndrome (SDS) is an inherited marrow failure syndrome associated with exocrine pancreatic dysfunction and an increased risk of myelodysplasia and leukemia. The majority of individuals with SDS carry biallelic *SBDS* gene mutations; however, a subset of patients remain genetically undefined. We investigated the clinical phenotype of genetically undefined SDS and compared to the features of patients with *SBDS* mutations. Since December 2008 the North American Shwachman-Diamond Syndrome Registry (SDSR) has collected clinical data on 55 individuals with biallelic *SBDS* mutations and 16 genetically undefined SDS patients who meet clinical diagnostic criteria. These two groups of patients shared overlapping and distinct clinical and hematopathological features. Cytopenias were present for both *SBDS* mutation positive and negative cohorts, with neutropenia the most common in 94% and 81% respectively. Bone marrow hypocellularity was reported in 91% of those with *SBDS* mutations and 69% of those without. Marrow dysplasia was reported in 65% of those with *SBDS* mutations and none of those without. Clonal abnormalities were present in 44% and 25% of those with and without *SBDS* mutations with median age of initial appearance of 9 years (0.8-45.1) and 7 years (1.2-14) respectively. Abnormalities included del7q and del20q in both groups as well is iso7q, trisomy 8 and others in the *SBDS* mutation-positive group. Clonal abnormalities were all transient in the *SBDS* mutation negative cohort. One *SBDS* mutation-positive individual developed AML. None of the *SBDS* mutation negative individuals developed malignancy or progressed to require HSCT thus far. Pancreatic dysfunction determined by low serum tryspinogen or pancreatic isoamylase was similar in both cohorts 79% vs 80%. However, only 27% (15/55) of *SBDS* mutation-positive individuals reported requiring enzyme therapy with 33% (18/55) documenting failure to thrive, in contrast to 75% (12/16) of *SBDS* mutation-negative individuals with 73% (11/15) having failure to thrive. A broad spectrum of congenital anomalies was reported in 55% and 56% of *SBDS* mutation positive and negative individuals respectively, with skeletal anomalies being the most common in both groups. The natural history of SDS into adulthood is also under investigation. The SDS Registry provides a resource to advance our understanding of the clinical presentation, natural history, disease pathogenesis, and treatment of this disorder.

SP-037

HOW MANY AND WHICH MOLECULAR MARKERS ARE REALLY NEEDED IN THE MANAGEMENT OF ACUTE LEUKEMIAS AND MDS?

Mehmet Yilmaz. *Gaziantep Üniversitesi Şahinbey Araştırma Ve Uygulama Hastanesi*

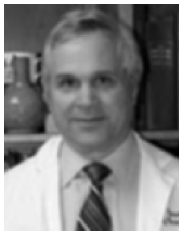
Acute myeloid leukemia (AML) is the most the most common acute leukemia diagnosed in adult patients. Although most patients respose to induction and consolidation chemotherapy most of them relapse after those regimens and after stem cell transplantation. All the treatment modalities still remain poor. New treatment approaches are necessary based on new the molecular markers in AML. In this way AML patients are matched to the most appropriate therapies according to prognostic risk and response to treatment. There are relatively small group of genetic molecular markers to predict outcome to direct therapy in AML. For example CBF translocations can help for favorable outcome with induction/consolidation and for sensitivity all trans retinoic acid and arsenic trioxide. FLT3 in combination with NPM1 or CEBPA can be used to predict outcome in normal karyotype AML. These markers also can be used to identify AML patients who will benefit from allogeneic stem cell transplantation. Recent studies have showed increasing number of somatic mutations in AML patients including mutations in TET2, ASXL1, IDH16, IDH2, DNMT3A, and PHF6. Several of these genetic abnormalities have been shown to have prognostic importance in AML patients.

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic malignancies characterized by clonal expansion of bone marrow myeloid cells with impaired differentiation Like AML genes involved DNA methylation; DNMT3A, IDH1/IDH2, and TET2 and in the regulation of histone function; EZH2, ASXL1, and UTX are recurrently mutated in MDS. Recent advances from sequencing studies suggest that multiple mutations are required for MDS initiation and progression to acute myeloid leukemia (AML).

SP-040

STEM CELL MOBILIZATION FOR AUTOLOGOUS TRANSPLANT: WAYS TO IMPROVE THE COLLECTION AND TO PREVENT THE FAILURE

Albert D. Donnenberg[1], Jay Raval[2], Linda R. Moore[3], Joseph E. Kiss[1,4].
[1]University of Pittsburgh School of Medicine, Department of Hematology Oncology, Pittsburgh, PA; [2]University of North Carolina, Department of Pathology and Laboratory Medicine, Chapel Hill, NC; [3]University of Pittsburgh Medical Center, Pittsburgh, PA; [4]Institute of Transfusion Medicine, Pittsburgh, PA



Introduction: Mobilized peripheral blood is the most widely used source of hematopoietic stem cells (HSC) for autologous hematopoietic cell transplantation. This lecture will focus on best practices for stem cell mobilization and collection as proposed by the American Society for Blood and Marrow Transplantation [1], the European Group for Blood and Marrow Transplantation [2] and other experts in the field.

Mobilization regimens: Single agent mobilization with recombinant nonglycosylated G-CSF (filgrastim) or glycosylated G-CSF (Lenograstim) is widely used for hematopoietic stem cell transplantation in non-Hodgkin's lymphoma (NHL), Hodgkin's Disease (HD) and multiple myeloma (MM). The recommended dose of filgrastim is 10 μg/kg/day until the collection is complete. G-CSFs deemed biosimilar to the original licensed agent are now available and appear to be equivalent in activity and toxicity profile [3]. Polyethylene glycol coupled filgrastim (Pegfilgrastim) has a greatly extended half-life and has had limited use for HSC mobilization. Adding chemotherapeutic agents (most commonly cyclophosphamide, etoposide or a disease-specific regimen) to cytokine mobilization may increase HSC yield and potentially decrease tumor burden but carries a greater risk of hospitalization for neutropenic fever than cytokine alone. Plerixafor, a CXCR4 antagonist, enhances the mobilizing effect of G-CSF and has rapidly gained acceptance for MM and NHL patients who have mobilized poorly. It is most commonly administered 6-11 hours before leukapheresis in patients who have received 4 days of G-CSF but have not adequately mobilized. Plerixafor has been effectively administered by algorithm to promote mobilization in patients with peripheral CD34 counts <20/μL following combined G-CSF/etoposide therapy [4].

Predicting mobilization: Single agent daily administration of G-CSF yields a very predictable mobilization course with peak WBC and CD34 counts occurring between days 4 and 6. The mobilization window is later (typically 8-10 days) and less predictable in patients mobilized with chemotherapy plus G-CSF.

The peripheral CD34 count immediately preceding leukapheresis together with the anticipated blood volume processed comprise the the best predictor of CD34 content of the apheresis product. At the University of Pittsburgh Cancer Center's Adult Blood and Bone Marrow Transplant program we have standardized on large volume collections using the Cobe Spectra. A large volume collection is completed over 4 hours and represents approximately three blood volumes. We routinely perform large volume leukapheresis because it facilitates collection of intermediate mobilizers (10-20 peripheral CD34+ cells/μL) [5], and because it is operationally efficient (2 patients can be leukapheresed per instrument per day). The risks of large volume leukapheresis are minimal in patients with adequate platelets and include hypocalcemia/hypomagnesemia induced tetany, which can be remediated by intravenous administration of calcium gluconate. We perform three-hour leukapheresis on patients with low platelets (<50,000/μL). Additionally, when patients are predicted to have an extraordinarily high collection, we run a "what if" scenario to determine the predicted collection over 3 hours. The prediction is discussed with the attending physician and a decision is made whether to collect for 3 or 4 hours.

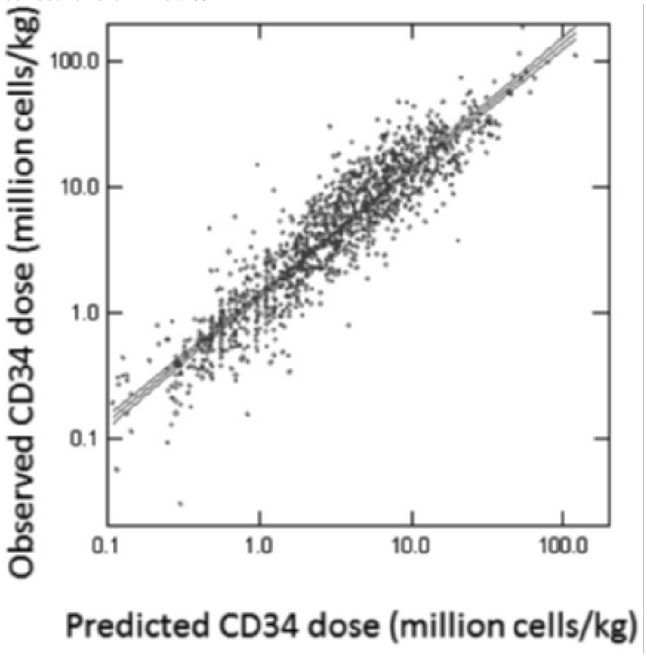


Figure 1. Predicted and observed CD34 dose in 1,257 leukapheresis collections of G-CSF mobilized autologous and allogeneic donors. Leukapheresis was performed the morning of the collection. The confidence bands indicate the 95% confidence interval about the regression slope (multiple $R^2 = 0.920$). CD34 content of peripheral blood and leukapheresis products was determined using a single platform assay (Beckman Coulter Stem Kit). The predictor, derived from multiple regression is:

log(CD34 dose)=5.169 + 0.986 × log(peripheral CD34 count) – 0.151 × (3 hr collection) – 0.028 × collection number – 0.058 × (male) + 0.077 × (autologous)

Where 3 hour collection = 1 if collection is 3 hours and 0 if it is 4 hours, male =1 if donor gender is male and 0 if gender is female, and autologous =1 if donor is autologous and 0 if donor is allogeneic. The effect of each parameter can be seen by the magnitude and sign of the respective coefficients.

Prediction is based on an algorithm developed and validated in-house on over 1000 observations (detailed in the legend to Figure 1). Significant independent predictors of collection by multiple regression are: log peripheral CD34 count, 3 versus 4 hour collection, collection number, autologous versus allogeneic donor, and gender. Of these, peripheral CD34 has the greatest influence by far. Prior to the first anticipated collection, a stat peripheral blood CD34 count is performed, and the leukapheresis team is notified of the predicted CD34 content (CD34/kg), including 95% confidence intervals. In our institution, leukapheresis is recommended if the lower confidence interval of the predicted CD34 dose exceeds 0.5 × 10^6 CD34+ cells/kg, but the attending physician makes the final determination. The predictor has been in use in our institution unmodified since 2003 and was initially based on independent training and validation sets. Figure 1 shows the correlation between the predicted and observed CD34 dose in the graft product. Defining an adequate leukapheresis collection as ≥ 2 × 10^6 CD34+ cells/kg, the algorithm predicts adequate collection with a sensitivity of 94.3%, specificity of 88.4%, positive predictive value of 95.4%, negative predictive value of 85.4% and a miscall rate of 7.4%. Figure 2 tabulates the proportion of patients collecting a given CD34 dose as a function of their peripheral CD34 count alone. From this analysis it is clear that it is futile to collect a patient with a peripheral count of less than 4 CD34+ cells/μL. When the peripheral count reaches 16-20 CD34+ cells/μL, all patients collected at least 1 × 10^6 CD34/kg, and 27% collected 1 × 10^6 or more CD34+ cells/kg.

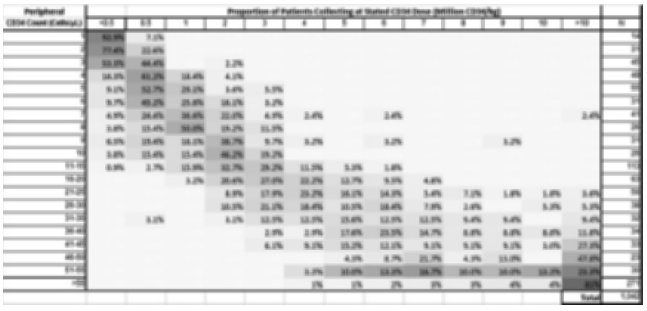


Figure 2. Peripheral CD34 count alone as a predictor of leukapheresis CD34 dose in a single leukapheresis. Data are based on peripheral CD34 counts of 1,042 patients obtained immediately prior to 4 hour large volume leukapheresis. The proportion of patients collecting at a given CD34 dose is shown as a function of the peripheral CD34 count on the day of leukapheresis (also indicated by the intensity of red shading).

A priori risk factors for poor mobilization include age greater than 60 years, a history of multiple chemotherapy regimens, exposure to alkylating agents or lenalidomide, prior irradiation and low platelet count. In our analysis peripheral CD34 count on the day of collection captures all of these risk factors (*i.e.* none were independent predictors when peripheral CD34 count was included in the model).

Since extensive resource use is associated with mobilization failures, several strategies have been tried to mobilize patients with low CD34 counts. Increasing G-CSF dose 2 to 3-fold, or twice daily G-CSF dosing have been investigated, with no clear cut recommendations emerging. Extending leukapheresis beyond four collections is also seldom successful. For initial mobilization failures, the risk of subsequent failure after 2-4 weeks of rest is high (>80%). Remobilizing with chemotherapy plus G-CSF is not only usually unsuccessful but adds toxicity. Where indicated by diagnosis, the European Group for Blood and Marrow Transplantation recommends administering preemptive Plerixafor in patients with pre-apheresis peripheral CD34 counts of <10 cells/μL. It recommends considering Plerixafor use in patients with peripheral CD34 counts between 10 and 20 cells/μL, taking into account other risk factors for poor mobilization as well [2]. Plerixafor is contraindicated in AML because has been shown to mobilize AML blasts in patients with refractory disease 2-3 fold, a property that has been exploited therapeutically [6].

Effect of total graft CD34 dose and multiple collections on engraftment: Although there is consensus that 2 × 10^6 CD34+ cells/kg is the minimum safe CD34 dose for an autologous leukapheresis graft product [1,2], both American and European consensus groups recommend higher doses (≥ 5 × 10^6 CD34+ cells/kg). Super mobilizers (>8 x 106/kg) have been shown to have faster engraftment, more durable platelet engraftment, and better overall and event free survival [7]. In our experience, performing multiple small collections which in aggregate meet a minimum target CD34 dose (2 x 10^6 CD34+ cells/kg) greatly increases the risk of delayed or failed platelet engraftment. It is worth mentioning that graft CD34+ cells are usually dosed on ideal body weight, as using actual body weight would result in one or more collections in 16% of patients, without measurably improving outcomes [8].

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SP-041

WHY: "NO" FOR ALLOGENEIC STEM CELL TRANSPLANTATION (ALLO-SCT) FOR ALL ADOLESCENTS/ADULTS WITH PHILADELPHIA NEGATIVE (PH-VE) ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN FIRST COMPLETE REMISSION (CR1)?

Mohammed Said Yousuf. *Ain Shams University Univ, Cairo, Egypt,Consultant, Team Leader, Leukemia and Procedure Clinics , KFSHRC, Riyadh, KSA*

Allo-SCT used to be associated with a better survival for adults with Ph-ve ALL in CR1 or beyond while chemotherapy used to be associated with relapse for the majority. In spite of the recent improvement in HLA typing, donor availability, and conditioning regimens, transplant related

mortality, sterility and acute and chronic GVHD remain unsolvable challenges.

Although a large metaanalysis [1] and a systematic review [2] suggested better survivals of adult ALL in CR1 after allo-HSCT when compared with chemotherapy even in standard risk ALL, the analyses were based on old studies utilizing adult-type or less intense chemotherapy protocols. Moreover, minimal residual disease (MRD) tool was not used for stratification and a significant bias was included in both.

With the recent adoption of pediatric-inspired chemotherapy protocols to adults up to the age of 40-60 years, many study groups reported an outcome as high as or even higher than allo-SCT for Ph-ALL in CR1 if they don't carry major adverse prognostic features like refractory disease, failure to achieve low minimal residual disease (MRD) or very poor risk cytogenetics [3-6]. The Swedish group [6] reported up to 47% 5 year overall survival in patients up to 46-79 years old after intensive chemotherapy with pragmatic use of MRD monitoring. GRAALL group [7] reported also that young to middle aged adults who received a pediatric intensive chemotherapy regimen don't appear to require allo-SCT if they achieve a good response on MRD after induction and that none of the good responders benefited from Allo-SCT than their counterparts who didn't receive allo-SCT.

Further investment in the four major assets of chemotherapy are expected to further improve none-transplant outcome of adult Ph-ALL in CR1, especially those with standard risk:

1. Comprehensive programs capable of delivering intensified chemotherapy with support services to manage complications, and improve compliance of both doctors and patients.
2. Utilization of MRD [8] tool to better stratification and select of those who may benefit from allo-SCT in CR1.
3. The addition of targeted monoclonal antibodies and immunotherapy (Rituximab, Blinatumomab (BiTE), Chimeric antigen Receptor T cell (CART) therapy [9,10].
4. Continuous research and collaborative trials trying to further understand molecular signatures and abnormalities that may prove targets for the new therapeutic modalities.

In conclusion, Allo-SCT should not be considered the first best option for all adults with Ph-ALL in CR1 and should be indicated only on individual basis and under the following conditions:

1. Inability to deliver or ineligibility for intensified pediatric inspired protocols
2. Those with refractory disease or persistent residual disease after induction and or consolidation
3. Relapsing ALL

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SP-044
RATIONAL DRUG USE AND THE PHARMACEUTICAL INDUSTRY

Canan Uluoğlu. *Gazi University, Medical Pharmacology*

Irrational drug use is not only our country's problem, but also a global public health problem. As a result of irrational use of drugs all around the world, the concept of rational use of medicine for the first time has been introduced by World Health Organization (WHO) conference of experts in Nairobi 1985 (1). The rational use of drugs has been described as patients should receive medications in compliance with their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community.

When rational use of medicine cannot be achieved, increased mortality and morbidity, increased adverse drug reactions and hospitalization, drug wastage, drug resistance, environmental pollution and wasted economical resources will occur.

According to WHO, physicians should follow the 6 steps to improve rational drug prescribing. (I) Identify the patient's real problem. This may be a specific problem as in infectious diseases or non specific or a drug's adverse effect, (II) determine the target of treatment such as to relieve pain, to eradicate bacteria or to improve quality of life (III) list possible intervention or treatment. This may be a non drug treatment or drug treatment. Drug must be chosen taking into account the parameters of efficacy, safety, suitability (high risk group of patients, contraindications, the diversity of the formulation etc.) and costs. Current diagnostic and treatment guidelines should be based. Special groups (children, elderly, pregnancy, breastfeeding women, patients with kidney and liver failure, history of drug/OTC/herbal or food allergies) should be interpreted with caution, (IV) (if necessary) start the treatment by writing an accurate and complete prescription e.g. name of drugs with dosage forms, dosage schedule. It is thought that common prescription errors are missing information, inappropriate choice of drug, incompatibility among drugs in prescription (drug –drug interactions), unreadable handwriting (if it is not e-prescription), (V) Given suitable information instruction and warning regarding the treatment such as total duration of the treatment, adverse effects of drug, dosage schedule, risk of stopping the therapy suddenly, drug storage conditions, contraception when using drug and cost of treatment, (VI) monitor the treatment, if necessary stop or change the treatment.

Although all these steps are the responsibility of the physician, physicians are only one of the responsible parties for rational use of drugs. Responsible parties are physicians, pharmacists, nurses, other medical staff, patients and patients' relatives, pharmaceutical industry, regulatory authorities and others (media, academia, the educational system etc.) for rational use of drugs.

Because so many parties responsible for the rational drug use, WHO suggests 12 national strategies to promote rational use of medicines (2).

1. A mandated multi-disciplinary national body to coordinate medicine use policies
2. Clinical guidelines
3. Essential medicines list based on treatments of choice
4. Drugs and therapeutics committees in districts and hospitals
5. Problem-based pharmacotherapy training in undergraduate curricula

6. Continuing in-service medical education as a licensure requirement
7. Supervision, audit and feedback
8. Independent information on medicines
9. Public education about medicines
10. Avoidance of perverse financial incentives
11. Appropriate and enforced regulation
12. Sufficient government expenditure to ensure availability of medicines and staff

On the other hand, things that need to be done to improve the rational use of medicines in 27 EU member states are summarized in six key title according to the "*Rational Use of Medicine in Europe Executive Summary Report*" published in February 2010 (3).

1. INN prescribing (International Nonproprietary Name NN)
2. Prescription guidelines
3. Pharmaceutical budgets for doctors
4. Promoting the use of generic drugs
5. Prescription monitoring
6. Information activities targeted at the general public.

In Turkey, people can buy drugs without prescription (except for controlled drugs), and so self-medication rates have been reported to be high, and can be the cause of wasted resources, the emergence of resistant strains of microorganisms, and serious adverse reactions. World Health Organization refers that at least half of the antibiotics consumed by humans is unnecessary (2). Overuse and misuse of antimicrobials contributes to antimicrobial resistance. A major issue of concern to hematologists is the intensive use of antibiotic in patients with immune suppressed, receiving chemotherapy, or undergoing bone marrow transplantation. For the first time, in a study including Turkey, validated data on antibiotic use in seven newly independent states (Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Moldova, Tajikistan), five southern and eastern European countries (Bosnia and Herzegovina, Croatia, Montenegro, Serbia, Turkey), and Kosovo, have been collected and analysed. This study provided publicly available total antibiotic-use data for 13 non-EU countries and areas of the WHO European region. (4). In this study, Turkey had the highest antibiotic use in Europe, and on the basis of this finding, the Turkish government already published a *Rational Drug Use National Action plan 2013–2017*, with quantitative targets to reduce antibiotic use. In fact, although positive developments accelerated in recent years, applications within the context rational drug use started at after 1990 in Turkey (5). Prescription monitoring and evaluation process is one of the interesting title among these activities. Physicians' prescriptions can be analyzed and evaluated and the feedback related them can be given by way of "*Prescription Information System*" which was developed to promote rational use of medicine in our country (6).

The pharmaceutical industry can contribute to rational drug use before prescribing process. It is important to creation and the implementation of marketing strategies and, appropriately storing and distributing of the drug. The responsibilities of pharmaceutical companies concerning rational use of drugs are also to provide clear and understandable drug leaflet, drug formulations in accordance with treatment guidelines and rational drug use, appropriate drug containers. On the other hand, some factors related to pharmaceutical companies can influence compliance of patients. Advertisements for OTC drugs can result in the patient stopping taking the "real" medication, or promotional activities of the pharmaceutical manufacturers may affect rational prescribing.

On the other hand**,** non-rational usage of drugs enhance the percent of medical cost in the health funds. Different methods are recommended to control the drug expenditure

all around the world:

- Implementation the principles of rational drug use
- Regulations relating to prescription writing
- Awareness for preventive and protective treatment
- Promoting the use of generic drugs (While original drugs offer a new, effective, and safe treatment to humanity, generic drugs constitute an economical alternative)

In conclusion, irrational use of medicines is a serious global public health problem. But, as stated by the World Health Organization "*Irrational prescribing is a difficult disease to cure, but prevention is possible*".

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SP-046

DIAGNOSIS AND MANAGEMENT OF PERIOPERATIVE RISK (BLEEDING AND THROMBOSIS)

Burak Uz. *Gazi University Faculty of Medicine, Department of Internal Medicine, Division of Adult Hematology, Beşevler, Ankara*

The main goal of this presentation is to assess a patient before an invasive procedure in terms of bleeding and thrombosis risk, or both. An excessive bleeding history including previous surgery and trauma, some conditions leading to bleeding tendency (e.g. liver disease, renal disease, myeloproliferative neoplasms), usage of anticoagulant/antithrombotic medications, and a positive family history should be questioned. These efforts will provide a rational and cost-effective approach to the effective use of coagulation screening profile in order to predict the bleeding risk during and/or after an invasive procedure.

Due to the complex physiology of the hemostatic mechanisms and widely used in vitro laboratory assays (e.g. PT, APTT) can not accurately reflect the in vivo hematologic response, the clinicians must interpret the coagulation tests with their limitations. Routine coagulation testing in unselected patients is not recommended (Grade B, Level III). Despite this evidence, generalized screening is prevalent. A structured bleeding history may be a good predictor of postoperative bleeding rather than an unstructured one (Grade B, Level III). For this purpose several bleeding history questionnaires have been validated and applied. If the bleeding history is negative, no further coagulation testing is endicated (Grade C, Level IV); whereas if the bleeding history is positive or there is a clear clinical indication, a comprehensive assessment is required (Grade C, Level IV) [1]. Therefore, it should be noted that the high-risk patients will require further testing.

For the prevention of venous thromboembolism (VTE) risk-stratification of each surgery patient (low, modest, high, highest) should be done on the basis of risk factors (modifiable/non-modifiable), and surgery type (general/abdominopelvic, orthopedic) or clinical presentation (acutely ill hospitalized patient) [2]. Pharmacological, mechanical or both forms of VTE prophylaxis strategies should be prefered with respect to the patient's characteristics and the type of surgery [3].

With every approach to reduce thrombosis risk, however, there is an accompanying risk of increasing bleeding complications. Conversely, reducing bleeding complications may increase thrombotic (ischemic) events. The benefit of pharmacologic thromboprophylaxis must always be weighted against the bleeding risk. The individual patient is at the center and optimal patient outcome should be its goal.

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