6th international ELN Workshop on Standardization of Flow Cytometry in MDS
October 31-November 2, 2013, Munich, Germany

Final report of the IMDSFlow WG

Summary

The working group (WP8/ELN) now referred to IMDSFlow has agreed that Flow Cytometry (FC) adds significantly to MDS characterization, diagnosis and prognosis. This is highlighted by the fact that FC is just fully incorporated in the ELN and the USA (version 2.2014 MDS) guidelines in diagnosis and treatment of MDS. It may also be useful in predicting and monitoring disease during treatment with new and standard therapeutic regimens. Repeated FC assessments are strongly recommended not only in cases such as ICUS and IDUS, but also to monitor the natural course of the disease in patients with untreated low and intermediate-1 risk MDS. The 6th international ELN Workshop on Standardization of FC in MDS was successfully held in Munich at MLL from Oct 31-Nov 2, 2013, and will continue its continuous efforts on fully implementation of FC as part of an integrated diagnostic approach. In the current workshop the implementation of dyserythropoiesis is further explored whereas an attempt is undertaken to fully integrate FC in the new WHO diagnosis of MDS.

Scientific content

Flow cytometry in MDS as a diagnostic tool

Patients classified by the WHO2001 as having dysplasia in two or three cell lineages (refractory cytopenia with multilineage dysplasia, RCMD) have significantly worse overall survival (OS) and increased risk of leukemic transformation than those with refractory anemia (RA), irrespective of the presence or absence of ring sideroblasts (RS). FC might help to dissect true RA from RCMD by identifying RA with immunophenotypic abnormalities in the myeloid compartment from RA with only erythroid dysplasia. The new WHO2008 classification identifies three separate entities within the MDS subgroup of refractory cytopenia with unilineage dysplasia (RCUD): refractory anemia (RA), refractory neutropenia (RN) and refractory thrombocytopenia (RT). This classification relies on the lineage displaying more than 10% of dysplasia, and either uni- or bi-cytopenia. It is unclear whether or not RA, RN, RT are distinct MDS subtypes with respect to survival or risk of leukemic transformation. Another newly defined subgroup of MDS is unclassifiable MDS or MDS-U where dysplasia is seen in less than 10% of cells in one or more lineages but associated to cytogenetic abnormalities. The role of FC within RCUD and MDS-U is not yet established but it might allow to identify different disease entities with different prognoses. Moreover, MDS-U patients should be separated from those with cytopenias, who do not meet the criteria of MDS (e.g. with normal karyotype) and have no other underlying condition that could explain cytopenia. This latter condition is now recognized as idiopathic cytopenia of undetermined significance (ICUS). In contrast to idiopathic dysplasia of undetermined significance (IDUS), patients with ICUS have no major dysplasia but are defined by unexplained cytopenia. IDUS can be considered as a potential pre-phase of MDS. FC could be of value to support the diagnosis IDUS, discriminate between IDUS and MDS and identify IDUS cases that will remain stable rather than progress to acute myeloblastic leukemia (AML) or myeloproliferative neoplasm. Finally, the WHO classification separates MDS with isolated del(5q) as a distinct entity since these patients are characterized by specific morphologic and clinical parameters and have a low risk of evolution to AML. FC may add information to identify 5q- patients with additional immunophenotypic abnormalities who may be at increased risk of evolving to overt AML. This would be important to properly assign these patients to treatment with lenalidomide. It has been shown in a prospective study that in cytopenic patients with a non-diagnostic BM, FC can effectively aid in distinguishing reactive or secondary chronic cytopenias from myeloid neoplastic diseases. A negative predictive value of 96% by FC could be achieved in patients without significant morphological dysplasia or cytogenetic abnormalities. In addition, FC aberrancies in immature progenitors are highly specific for diagnosing MDS albeit with a lower sensitivity. Recently, a FC test to diagnose low risk MDS

patients was designed based on four cardinal parameters i.e the percentage of myeloid progenitors, B cell progenitors, CD45 expression on myeloid progenitors and neutrophil hypogranularity as assessed by sideward light scatter (SSC), which could be confirmed in a multicenter study. Results revealed a sensitivity of 70% and a specificity of 92%.

Flow cytometry in MDS and prognosis

It has been shown that granulocytic and monocytic dyspoiesis in MDS, identified as immunophenotypic abnormalities by FC, correlates with the International Prognostic Scoring System (IPSS), the WHO-adjusted prognostic scoring system (WPSS), transfusion dependency, and time-to-progression to advanced MDS/AML as well as with outcome after hematopoietic stem cell transplantation. Immunophenotypic aberrancies on myeloid progenitors may also have an independent prognostic impact even if the percentage of blasts in the BM is below 5%. The IPSS represents the benchmark for clinical trials and treatment decision-making in MDS. IPSS is currently under extensive re-evaluation with notably a re-categorization of cytogenetic aberrations. IPSS also does not include yet newly defined prognostic parameters such as co-morbidity scores, serum LDH, BM fibrosis, circulating blasts (normal or aberrant), methylation status, single nucleotide polymorphisms analysis (SNP), mutational status and transfusion requirements. It was shown recently, that cytogenetic abnormalities typically associated with MDS, such as monosomy 7, del(5q) and complex cytogenetics are correlated with an increased flow cytometric score (FCSS $\geq$2), whereas chromosomal abnormalities such as trisomy 8, del(20q) and loss of Y, which may also occur in other hematological neoplasms, more frequently display lower FCSS. This confirmed previous data that among patients with lower risk MDS, FC abnormalities were less prominent in patients with trisomy 8 or del(20q). Moreover, the number of FC aberrancies identified in MDS has been reported to be associated with OS, The FCSS extends the prognostic utility of FC assessment especially in RCMD. Although the (revised)-WPSS provides an extended prognostic algorithm compared with the IPSS, FC may further refine this prognostic model. Evidence for the role of immune dysregulation in MDS pathogenesis is becoming stronger. Indeed, the number and functional status of $CD4^+$ and $CD8^+$ T-cells, NK cells and monocytes are correlated with disease severity. These features also allow differentiating between low risk MDS and aplastic anemia. These markers may add to the FC platform but are not yet included routinely.

Flow cytometry in predicting and monitoring treatment response and disease progression in MDS

The presence of immunophenotypically aberrant myeloid progenitors is instrumental in predicting the response to growth factor treatment. Patients with low serum erythropoietin (Epo) and immunophenotypically normal myeloid progenitors have a high probability (94%) to respond to growth factors. By contrast, patients with aberrant myeloid progenitors and/or high serum Epo levels have a low probability (11%) to respond to treatment. In addition, the degree of phosphorylation of ERK as assessed by FC correlates with response to Epo treatment and OS in low/int-1 risk MDS. (3Disease monitoring by FC may be important especially when other disease parameters such as hematological, molecular and cytogenetic parameters are normal or uninformative about the expected response to therapy. Preliminary studies indicate that MDS-related FC abnormalities in BM cells are no longer detectable or have decreased in responding patients when compared to pre-treatment results. Stable or increased FC aberrancies during treatment may spare patients from long-term treatment with ineffective drugs. This may be of importance in patients treated with hypomethylating agents such as azacitidine who may benefit from an increased OS. Studies are currently ongoing to identify, by intensive FC monitoring, patients who may benefit from prolonged treatment with azacitidine.

the 5th international ELN Workshop on FC and diagnostics: At least half of the activities of the working Group at the 5th meeting (2012) focuses on the current implementation of the proposed FC guidelines for diagnosis of MDS in Japan, France, The Netherlands and in the UK. Although, still major differences between labs and countries are existing, the data as provided indicate that FC may add significantly to the diagnosis of MDS especially in those patients in which the current diagnostic procedures fail. In this respect, FC may support the diagnosis or even may add to the exclusion of MDS in patients with mild cytopenia. In addition, it was discussed in detail which emerging parameters might be of value in this diagnostic approach in which the focus still should be a widely applicable and robust tool. New software technologies as developed by the Euro-Flow consortium might add significantly to the performance of the use of FC in diagnosis of MDS. Regarding new parameters in this respect, the analysis of the erythroid development was intensively discussed by presenting the collectively analysed data set of the group. Several distinct subpopulations within the dysplastic erythropoiesis are recognized as associated with MDS. Finally, the role of FC in dysplastic thrombopoiesis was discussed; with

respect to mature thrombocytes, new parameters are emerging which are of potential interest to add to the multiparameter and multidimensional FC approach of MDS.

Perspectives from the 5th international ELN Workshop on FC and prognosis: It is clear that FC may add significantly in the identification of MDS subgroups defined by the current IPSS, WPSS and also the IPSS-revised scoring systems; The major problem is which parameters are more or less important in predicting prognosis and how should this be implemented in the current emerging era of therapeutic developments. To start from this, several groups will analyse their own data set with respect to clinical prognostic features upon the basic ELN platform. In addition, the role of molecular markers in the context of FC parameters will be investigated preferable within prospective clinical setting. The results provided by the WP8 of the ELN have major impact on new diagnostic strategies in MDS. The Pavia meeting of 2011 has gained the first steps in defining dyserthropoiesis by flow cytometry which is translated to prospective multicenter studies which might be of particular importance since new drugs are emerging in both lower and higher risk MDS. In addition, the Working Group may provide evidence that FC may add in new prognostic scoring systems. The Amsterdam Meeting in 2012 has focused on evaluating the just initiated prospective multicenter studies to emphasize diagnostics and prognostics in MDS which might be included in the new WHO classification of hematopoietic neoplasms. In addition, the ELN guidelines just published in Blood (Malcovati et al.,) identified flow cytometric assessment as one of the recommended approached in the diagnostic work-up. This years meeting will be organized by guest-chair Dr. W. Kern from MLL (Munich Leukemia Labor) Oct 31-Nov 1, 2013.

Selected References list from the ELNet WP 8 flow group: 2009-2013 after its initiation in 2008

1. Loosdrecht AA van de, Alhan C, Bene C, Dräger A, Della Porta M, Feuillard J, Font P, Germing U, Haase D, Homburg C, Ireland R, Jansen J, Kern W, Loken M, Malvovati L, Marevelde J te, Mufti G, Ogata K, Orfao A, Ossenkoppele GJ, Porwit A, Preijers F, Richards S, Schuurhuis GJ, Subira D, Valent P, Velden V van den, Westra G, Witte T de, Wells DA, Westers TM. Standardization of flow cytometry in myelodysplastic syndromes: report form the first ELNet working conference on flow cytometry in MDS. **Haematologica 2009:94:1124-1134.**

2. Della Porta MG, Picone C, Malcovati L, Pascutto C, Tamura H, Handa H, Czader M, Freeman S, Vyas P, Porwit A, Saft L, Westers TM, Alhan C, Cali C, Van de Loosdrecht AA, Ogata K. Multicentric validation of a reproducible flow cytometric score for the diagnosis of low-risk myelodysplastic syndromes: results of a European LeukemiaNET study. **Haematologica 2012;97:1209-17.**

3. Westers TM, Canan Alhan, Jan Sebastian Balleissen, Marie Christine Béné, Peter Bettelheim, Kate Burbury, Matteo G Della Porta, Angelika M Dräger, Jean Feuillard, Patricia Font, Ulrich Germing, Detlef Haase, Robin Ireland, Ulrike Johansson, Wolfgang Kern, Shahram Kordasti, Michael R Loken, Luca Malcovati, Jeroen G te Marvelde, Sergio Matarraz, Timothy Minle, Bijan Moshaver, Ghulam J Mufti, Kiyoyuki Ogata, Alberto Orfao, Anna Porwit, Katarina Psarra, Stephen J Richards, Dolores Subirá, Vicky Tindell, Theresa Vallespi, Peter Valent, Vincent HJ van der Velden, Theo M de Witte, Denise A Wells, Florian Zett, Arjan A van de Loosdrecht. Standardization of Flow Cytometry in Myelodysplastic Syndromes: A report from an International Consortium and the European LeukemiaNet Working Group. **Leukemia 2012;26:1730-41.**

4. Westers TM, Vincent HJ van der Velden, Canan Alhan, Roelof Bekkema, André Bijkerk, Rik Brooimans, Claudia Cali, Angelika M Drager, Roger K. Schindhelm, Christa Homburg, P (Ellen) A Ellen Kuiper-Kramer, Marije Leenders, Ingrid Lommerse, Jeroen G te Marvelde, Joke K van der Molen-Sinke, Bijan Moshaver, Frank WMB Preijers, Alita van der Sluijs, Elisabeth R van Wering, August H Westra, Arjan A van de Loosdrecht. Implementation of Flow Cytometry in the Diagnostic Work-Up of Myelodysplastic Syndromes (MDS) in a multicentre approach:Report from the Dutch Working Party on Flow Cytometry in MDS. **Leuk Res 2012;36:422-30.**

5. Loosdrecht AA van de, Canan Alhan, Jan Sebastian Balleissen, Marie Christine Béné, Peter Bettelheim, Kate Burbury, Matteo G Della Porta, Angelika M Dräger, Jean Feuillard, Patricia Font, Ulrich Germing, Detlef Haase, Robin Ireland, Ulrike Johansson, Wolfgang Kern, Shahram Kordasti, Michael R Loken, Luca Malcovati, Jeroen G te Marvelde, Sergio Matarraz, Bijan Moshaver, Ghulam J Mufti, Kiyoyuki Ogata, Alberto Orfao, Anna Porwit, Katarina Psarra, Stephen J Richards, Dolores Subirá, Vicky Tindell, Theresa Vallespi, Peter Valent, Vincent HJ van der Velden,Theo M de Witte, Denise A Wells, Florian Zettl, Theresia M Westers. Rationale of Flow Cytometry in Myelodysplastic Syndromes: Position paper of the European LeukemiaNet working group on flow cytometry (WP8). **Leukemia and Lymphoma 2013:54:472-5.**

6. Loosdrecht AA van de, Westers TM. Cutting edge: flow cytometry in myelodysplastic syndromes. **J Natl Compr Canc Netw. 2013 Jul;11(7):892-902.**

Assessment of results and impact of the meeting on the future direction of the field in 2013-2014

Results of the 6th international ELN Workshop on FC in MDS

The 6th 2013 meeting was dedicated to intensive discussions on the full implementation of FC in integrated reporting of patients with cytopenias and/or MDS. Since both the ELN guidelines as well as the USA guidelines,

published in Blood (Malocovati L et al.,) and the J Natl Comp Canc Netwerk, (Greenberg P et al) respectively, highlight the need for FC in MDS, the impact of our group is really high to further improve the quality and added value of this innovative strategy. Therefore, guided by A. Porwit and M.C. Bene, in this years meeting we prepared the text for a manuscript discussing the role of FC in the WHO2008 diagnostic structure. To this end a manuscript of our WG is under consideration to publish [re-submitting after 1st review before March 1, 2014] in an outstanding European Journal. (see also table 1 attached from Leukemia 2012;26:1730-41)

Malcovati L, Hellström-Lindberg E, Bowen D, Adès L, Cermak J, Del Cañizo C, Della Porta MG, Fenaux P, Gattermann N, Germing U, Jansen JH, Mittelman M, Mufti G, Platzbecker U, Sanz GF, Selleslag D, Skov-Holm M, Stauder R, Symeonidis A, van de Loosdrecht AA, de Witte T, Cazzola M. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013;122:2934-64.

Greenberg PL, Attar E, Bennett JM, Bloomfield CD, Borate U, De Castro CM, Deeg HJ, Frankfurt O, Gaensler K, Garcia-Manero G, Gore SD, Head D, Komrokji R, Maness LJ, Millenson M, O'Donnell MR, Shami PJ, Stein BL, Stone RM, Thompson JE, Westervelt P, Wheeler B, Shead DA, Naganuma M. Myelodysplastic syndromes: clinical practice guidelines in oncology.
J Natl Compr Canc Netw. 2013 Jul;11(7):838-74.

Table 1: Westers TM, et al. Leukemia 2012;26:1730-41

Diagnostic tool	Diagnostic value	Priority
Peripheral blood smear	• Evaluation of dysplasia in one or more cell lines • Enumeration of blasts	Mandatory
Bone marrow aspirate	• Evaluation of dysplasia in one or more myeloid cell lines • Enumeration of blasts • Enumeration of ring sideroblasts	Mandatory
Bone marrow biopsy	• Assessment of cellularity, CD34+ cells, and fibrosis	Mandatory
Cytogenetic analysis	• Detection of acquired clonal chromosomal abnormalities that can allow a conclusive diagnosis and also prognostic assessment	Mandatory
FISH	• Detection of targeted chromosomal abnormalities in interphase nuclei following failure of standard G-banding	Recommended
Flow cytometry immunophenotype	**• Detection of abnormalities in erythroid, immature myeloid, maturing granulocytes, monocytes, immature and mature lymphoid compartments**	**Recommended* If according to ELN guidelines**
SNP-array	• Detection of chromosomal defects at a high resolution in combination with metaphase cytogenetics	Suggested (likely to become a diagnostic tool in the near future)
Mutation analysis of candidate genes*	• Detection of somatic mutations that can allow a conclusive diagnosis and also reliable prognostic evaluation	Suggested (likely to become a diagnostic tool in the near future)

As can be seen in the attached agenda the focus in 2013 was how to implement diagnostic flow cytometry criteria to define dyserythropoiesis. Since, an independent group of French investigators in which 1 of our members was involved just published about a FC approach {Mathis S, et al., Leukemia 2013;27:1981-198} we extensively discussed how to use the ELN WG data set. Strikingly, the assumed parameters were already identified by our WG for some years [CD36/CD71] and a re-analysis of the data set was presented. It was decided that the current erythroid data set comprising of > 400 samples will be updated and that a draft manuscript will be written in q1-2014. In addition, this approach will be implemented in the so-called Ogata score for diagnosis of MDS. Finally, extensive discussion focuses on dystrombopoiesis. There are still several issues remaining dealing with artefacts due to activation of samples after obtaining the samples from patients. It was decided that in the upcoming year optimal technical assesements will de performed before extending towards a multicenter ELN approach. Finally, the outcome of the meeting has already been discussed at

ASH2013 in New Orleans and will be presented at the WP8 subcommittee meeting in Mannheim 2014. A summary slide and an achievements slide presented at ASH2013 are attached below. The 7th meeting of the ELN FC WG within WP8 is scheduled at Vienna Oct 30-31, Nov 1, 2014 {guest chair; prof.dr.P. Bettelheim}.

Activities and Perspectives of FCM in MDS: *2014*

VU medisch centrum

- Full Implementation in an **integrated diagnostic report** including prognostic value of FCM results **[Loosdrecht AA van de, et al., ongoing]**
- FCM should be part of the **next** WHO-classification **[Porwit A, et al., submitted]**
- Identification of **prognostic subgroups** in MDS specific disease entities [i.e. (del)5q] **[initial report from a multicenter study Oelschlaegel U, et al., submitted]**
- confirmation of FCM results in (**dys)erythropoiesis** in 2014 **[Westers TM, et al., in preparation]**
- Validation of FCM in a *IMDSFlow* **multicenter study** **[Kern W, et al., ongoing]**
- Validation of FCM in MDS in **prospective multicenter** clinical trials **[Cremers E, et al., and Burbury K, et al., ongoing]**
- Explorative studies on **(dys)megakaryopoisis** by FCM **[Matarraz et al., ongoing]**

VU Hematologie

Achievements of IMDSFlow WG on FCM in MDS since start in 2008 → 2013

VU medisch centrum

- **publications from the iMDSFlow WG [WP8/WP10]: 6 reports**
- Loosdrecht AA van de, et al., Haematologica 2009; 94;1124
- Westers TM, et al., Leukemia 2012;26:1730-41
- Della Porta M, et al., Haematologica 2012;97:1209-17
- Loosdrecht AA van de, et al., Leuk Lymphoma 2013;54:472-7
- Loosdrecht AA van de, et al., MDS Foundation News Letter 2013;19:2-4
- Porwit A, et al. (submitted)

- ***spin-off publications of individual groups members of iMDSFlow WG: >25 reports***
- Ogata K, et al., Haematologica 2009;94:1066-74
- Satoh C, et al., Leuk Res 2009:33:326-31
- Matarraz S, et al., Clin Cytometry 2010;78:154-68
- Kern W, et al., Cancer 2010;116:4549-63
- Westers TM, et al., Blood 2010;115:1779-84
- Valent P, et al., Oncotarget 2010;1483/96
- Chu SC, et al., Leuk Res 2011:35:868-73
- Ogata K. Leuk Res 2011:35:848-9
- Ossenkoppele GJ, et al., Br J Haematol 2011:153:421
- Cutler J, et al., Clin Cytometry 2011;80:150-57
- Della Porta M et al., Clin Cytometry B 2011:80;201-11
- Loosdrecht AA van de, et al., Leuk Res 2011:35:850-2
- Porwit A. Semin Diagn Pathol 2011;28:273-82
- Westers TM, et al., Leuk Res 2012;36:422-30
- Ogata K et a;., Leuk Res 2012;36:1229-36
- Sandes AF, et al., Haematologica 2012;26:1730-41
- Matarraz S, et al., PlosOne 2012; e44321
- Bellos F, et al., Cytometry B Clin Cytom 2012;82:295-304
- Oelschlaegel U, (Parmentier S) et al., Ann Hematol 2012;91:1979-81
- Kern W, et al., Haematologica 2013;98:201-7
- Malcovati L, et al., Blood 2013;122:2943-64
- Kern W, et al., Cytometry B Clin Cytom 2013;84:194-7
- Wangen JR, et al., (loken MR) Int J Lab Heamatol 2013;oct 3 [epub ahead of print]
- Burbury KL, et al., Leuk Lymphoma 2013;aug 20 [epub ahead of print]
- Alhan C, et al, Cytometry B clin Cytom 2013 (re-submitted)
- Loosdrecht AA van de, et al., J Natl Compr Cancer Netw 2013;11:892-902

VU Hematologie

Final programme 2013; MLL Munich, Germany

Thursday 31 October 2013

Arrival at Munich

19.00 – 22.00 ***Reception in Munich*** www.trattoria4mori.de

Friday 1 November 2013

MLL Münchner Leukämielabor GmbH
Max-Lebsche-Platz 31
81377 München, Germany
(www.mll.com)

08.30 - 09.00	***Registration and coffee***
09.00 - 09.15	Welcome and outline of the workshop W. Kern (G), A.A. van de Loosdrecht (NL)
09.15 – 09.45	***New standards in diagnostics and prognostic score in MDS****: A clinical perspective 2014* A.A. van de Loosdrecht (NL)
09.45 – 11.00	***Perspectives on the Implementation of flow cytometry in the diagnosis of MDS (discussion session)*** Chairs: T.M. Westers (NL) and W. Kern (G) This session is attempted to be highly interactive to make advantage of the current knowledge of all experts participating based on questions prepared by the chairs of the session
11.00 - 11.30	***Tea and Coffee***
11.30-12.45	***Integration in clinical reporting of flow in the diagnosis of MDS (discussion session)*** Chairs: R. Ireland (UK) and A. Porwit (C) This session is attempted to be highly interactive to make advantage of the current knowledge of all experts participating based on questions prepared by the chairs of the session

12.45 – 14.00	***Lunch at MLL with view on the Alps***
14.00 - 15.30	***Dyserythropoiesis 2013*** Chair: M.C. Bené (F) a) (dys)-erythropoiesis: flow meets molecular biology (P. Bettelheim, A) b) (dys)-erythropoiesis: a flow approach (M. Loken, USA) c) Current DataBase of ELN on (dys)-erythropoiesis (T.M. Westers, NL)
15.30 -16.00	***Tea and Coffee***
16.00 – 17.30	***Dysery- (cont'nd) and dystrombopoiesis*** Chair: M. Loken (USA) d) Proposal of an erythroid diagnostic score: discussion of draft proposal (M.C. Bene, F) ***(Dys)thrombopoiesis in MDS: how to start!*** e) Proposal and start of a multicenter study on PB dystrombocytopoiesis (S. Matarraz, S) ***General lecture on software in FC*** f) Kaluza Radar application (M.C. Bene, F)
19.30 – 22.30	***-Mahlzeit- in Munich*** (http://www.spurwechsel-muenchen.de/gallerie/partytram/)

Saturday 2 November 2013

09.00 - 10.30 **Diagnostic flow parameters**

Chair: K. Psarra (G)

a) The Multicenter study of ELN; *the first interim* analysis (W. Kern, G)

b) Cytopenia/MDS: role of flow in pediatric BM-failure (V. van der Velden, NL)

c) A 10-color 14 antibody tube that can be used for Ogata score screening (A. Porwit, C)

d) A reconciliation between Ogata Score and FCSS (L. Broderson, USA)

10.30 - 11.00 ***Tea and Coffee break***

11.00 - 12.30 **Flow cytometry in current prospective clinical MDS trials**

Chair: D. Subira-Perez (S)

a) added value of flow within a prospective clinical trial in low/int-1 risk MDS; the first results of HOVON89 (E. Cremers, NL)

b) response monitoring in clinical trials (K. Burbury, AUS/by Teleconferencing)

c) A Proposal for *FC-text* for the new WHO classification (A. Porwit/A.A. van de Loosdrecht, NL)

12.30 - 13.30 ***Lunch***

13.30 – 14.30 **Application of flow cytometry in MDS**

Chair: M. DellaPorta (I)

a) Lineage Infidelity of progenitor cells: impact on Ogata score? (K. Ogata, J)

b) Pitfalls in the Clinical Utility of Ogata score: an independent cohort study (J. Feuillard, F)

c) M-ferritin and sideroblastic MDS: role of SF3B1 (M. Della Porta, I)

14.30 – 15.00 **The future of flow cytometry in MDS**

Chair: T.M. Westers (NL)

a) Comparison of flow and genetic profiling (R. Ireland, UK)

b) Agenda for the next meeting 2014 (all)

Concluding remarks: A.A. van de Loosdrecht (NL) and

closure of meeting

Funding by ESF/ELN:

EFS was asked to support for E 2.000,- as part of the total budget of 16.000,- Euro. We have invited approximately 30 participants mainly from Europe for a 2-day conference with a 2-night stay at a hotel Thalmair nearby MLL Munich Labor (MLL), Munich, Germany. The meeting was supported by MLL Munich labor, Coulter, Germany, Celgene and Novartis. Participants pay for travel expenses by themselves/departments as in previous years.

Curriculum Vitae of Chair: prof.dr. A.A. van de Loosdrecht, Amsterdam, Netherlands

A.A. van de Loosdrecht (born: 09-10-1963) passed Medical School (cum laude) in 1989 at the VU University Medical Center in Amsterdam (VUmc), The Netherlands. After a 4th years scientific laboratory training in cell biology, immunology and hematology he received his PhD graduation (cum laude) in 1993 at the department of Hematology (VUmc) on the thesis; 'Monocyte mediated cytotoxicity in acute myeloid leukemia; Mechanisms and clinical implications'. In 1995 he graduated in Immunology (Msc). From 1993-1998 he followed clinical training in Internal Medicine followed by a fellowship in hematology (Department of Internal Medicine and Hematology at the Groningen University Medical Center, Groningen, Netherlands). From 2000, he is a staff member, Since 2009 he is an associate professor of hematology followed as a full professor at the department of Hematology, VUmc, Amsterdam (head: Prof.dr. P.C. Huijgens). The department of hematology at VUmc is incorporated in the Amsterdam School of Oncology, which has been approved by the Royal Netherlands Academy of Arts and Sciences. The department is one of the largest institutions in the Netherlands for the treatment of hematological malignancies. At present, the department has a leading role in the implementation of minimal residual disease detection using immunophenotypical methods in clinical protocols on leukemia of the HOVON/SAKK collaborative groups.

At the VUmc he is chair of the Scientific Committee (CWO) of the Institute of Cancer and Immunology (V-ICI). He is author of over 150 peer-reviewed papers published in national and international journals particularly in the field of hematology (myeloid malignancies) and immunology. He is reviewer of several national and international journals including Lancet, Leukemia, Blood, Leukemia Research, European Journal of Hematology, Britisch Journal of Hematology, Haematologica, Cellular Oncology, Journal of Cellular Biochemistry and Immunobiology. He is a member of European and American Society of Hematology (EHA, ASH), European Leukemia Net (ELN), the MDS foundation, European Macrophage and Dendritic cell Society (EMDS), International Histiocyte Society and national Societies in Hematology, Cytometry and Immunology (NVvH, NvC, NVvI).

His particular scientific experiences and interests are on translational hematology. He is projectleader/principal investigator of the preclinical and translational immunotherapy programs in myeloid leukemia (AML, CML) and myelodysplastic syndromes (MDS) since 2001 at the department of Hematology at VUmc Amsterdam together with prof.dr. G.J. Ossenkoppele and trained in GCP. The major research lines focus on the development of leukemic dendritic cell vaccines for active specific immunization in patients with minimal residual disease (MRD) in AML and MDS. To this a firm collaboration exists with Dr. T.D. de Gruijl, at the department of medical Oncology, Vumc, V-ICI, Amsterdam. In addition, effective antigen presentation of leukemic blasts, especially the role of MHC class II antigen presentation and class II-associated invariant chain peptide (CLIP) expression, their functional impact, regulatory mechanisms and modulation is a major focus of research. With respect to the latter a firm collaboration has been established with Dr. S.M. van Ham at the department of Immunopathology, Sanquin Research at CLB, Amsterdam and with Professor S. Ostrand-Rosenberg at Department of Biological Sciences, University of Maryland Baltimore County (UMBC) in USA. He is project leader/principle investigator of clinical (translational) programs dealing with the treatment of low-intermediate risk MDS with regimens containing erythropoietin and granulocyte-colony stimulating factors (Epo/G-CSF). Besides the clinical efficacy of Epo/G-CSF in MDS, research has focused on the potential immuno-regulatory capacity of erythropoietic proteins with respect to modulation of immunogenicity of hematopoietic precursor cell subpopulation. In addition, research focus on the role of flow cytometry in the diagnosis, prognostication and monitoring of MDS. He is chair of the working group MDS of the Dutch Society of Cytometry on the implementation of flowcytometry in MDS and initiated a platform within the ELN on the implementation of flowcytometry in MDS in Europe and abroad.

Selected publications of organizer and chair Prof. Dr AA van de Loosdrecht: see also ELNet related publications as cited above [see also pubmed.com]

1. Malcovati L, Hellström-Lindberg E, Bowen D, Adès L, Cermak J, Del Cañizo C, Della Porta MG, Fenaux P, Gattermann N, Germing U, Jansen JH, Mittelman M, Mufti G, Platzbecker U, Sanz GF, Selleslag D, Skov-Holm M, Stauder R, Symeonidis A, van de Loosdrecht AA, de Witte T, Cazzola M. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013; 122:2934-64.
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