Fifth international ELN Workshop on Standardization of Flow Cytometry in MDS
October, 26-27, 2012, Amsterdam, Netherlands

Final report (14-12-2012) by A.A. van de Loosdrecht, chair

Summary

The working group has agreed that flow cytometry (FC) adds significantly to MDS characterization, diagnosis and prognosis in the first 5 years of its existence within WP8 of ELN. 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 same holds true for patients treated with currently available drugs, preferably within clinical trials as conducted by national and international collaborating groups. The Fifth international ELN Workshop on Standardization of Flow Cytometry in MDS held in October, 26-27, 2012, Amsterdam, Netherlands, further focuses on widespread implementation of the diagnostic power and pitfalls in the diagnostic work-up of MDS as well establishing the prognostic value of MDS. To reach this goal several prospective trial initiatives are proposed and will be positioned within the next 1-2 years.

Scientific content and background of the meeting

Flow cytometry in MDS as a diagnostic tool

Background: 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%.

New perspectives from the 5th international ELN Workshop on FC and diagnostics: At least half of the activities of the working Group at this years' meeting (see program) focuses on the current implementation of the proposed FC guidelines for diagnosis of MDS. We discussed the current activities within 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, the group 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. Finally, 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. It was decided to increase the data set by adding additional samples to the cohort (>600 samples); after re-analysis by the Dutch group a document will be written which will be submitted for publication to a high

impact journal. 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. The Spanish group will coordinate the next steps to establish a robust flow protocol for multicenter use and evaluation.

Flow cytometry in MDS and prognosis

Background: 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.

New perspectives from the 5th international ELN Workshop on FC and prognosis: After discussing in detail the new IPSS-revised prognostic system for MDS the group discussed the impact of FC parameters in prognostication. 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 i.e. the HOVON89 study within the Netherlands dealing with low and int-I risk MDS patients (see also www.hovon.nl). It should be stressed that we need still 1-2 years before these data will be available to make any conclusions. Finally, it was discussed that the FC is not yet part within the integrated diagnostic approach regarding risk assessments.

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

Background: 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.

Perspectives from the 5th international ELN Workshop on FC and prediction of response: More mature data are discussed regarding the role of FC in predicting response to current new drugs used in the treatment of lower and high risk MDS. Although, the data are still sparse, the group identifies the FCSS as a tool for predicting response. It is too preliminary too recommend FC as a routine tool unless more data are emerging.

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

The results provided by the WP8 of the ELN have major impact on new diagnostic strategies in MDS. The last 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. To this end 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 main focus in 2012** has dealt with minimal diagnostic flow cytometry criteria to define dyserythropoiesis; It is anticipated that the working group will provide the first flow guidelines on this focussed subject which will thereafter be presented at ELN meetings in 2013 and will be prepared for publishing. In addition, in the almost finalized diagnostic and therapeutic guidelines in MDS as provided by WP8, flow cytometric assessment is now recognized as one of the recommended approached in the diagnostic work-up. Finally, as can be depicted from the reference list below, the working group is successful in translating the workgroup conferences into published documents on behalf of ELNet. The

next meeting will be organized by guest-chair Dr. W. Kern from MLL Munich Leukemia Labor, Germany in q4 2013.

Selected References list from the ELNet WP 8 flow group: 2009-2012 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. **Hematologica 2012;97:1209-17.**

3. Theresia M Westers, 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. Theresia M Westers, 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: [epub ahead of print per Oct5; 2011 (on line)].**

5. Arjan A van de Loosdrecht, 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 2012: [epub ahead of print per sept 14; (on line)].**

Spin-off publications of the ELN group as per2009 within WP8 MDS and Flow Cytometry

- 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
- 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
- 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
- Oelschlaegel U et al., Ann Hematol 2012; [epub ahead of print]
- Kern W, et al., Haematologica 2012; [epub ahead of print]

Final Program as followed actually at meeting

Thursday 25 October 2012

Arrival at Amsterdam WestCord Fashion Hotel (www.westcordhotels.nl)

19.00 – 22.00	***Reception in Amsterdam SKYY bar (10th Floor) WestCord Fashion Hotel***

Friday 26 October 2012

08.30 - 09.00	***Registration and coffee***
09.00 - 09.15	Welcome and outline of the workshop T.M. Westers, A.A. van de Loosdrecht (NL)
09.15 – 09.45	Introduction: ***Current concepts in diagnostics and prognostics in MDS***: *IPSS-revised, cytogenetics and mutational status* Chair: R. Ireland (UK) a) MDS: IPSS-revised and more [A.A. van de Loosdrecht](NL)
09.45 – 11.00	***Implementation of the flow-diagnostic score in MDS*** Chair: K. Ogata (Japan) a) **Introduction and Impact** of the *Ogata score* in Japan [K. Ogata](Japan) b) **Implementation** in the Netherlands [E. Cremers](NL) c) **Implementation** in France [J. Feuillard](F)

11.00 - 11.30	***Tea and Coffee***
	Chair: A. Porwit (Canada)
11.30 -12.45	d) **Implementation** in King's London [R. Ireland](UK)
	e) **Progenitor cells** by FC *versus* –blasts- by IHC and cytology [L. Saft](S)
	f**) Pitfalls** in the current diagnostic score [T.M. Westers](NL)
12.45 – 14.00	***Lunch***
14.00 - 15.30	***Dyserythropoiesis***
	Chair: M.C. Bené (F)
	a) FC and gene network of erythropoiesis [P. Bettelheim](A)
	b) Erythroid data of the ELN working group[T.M. Westers]
	c) Pitfalls/technical considerations [U. Johansson](UK)
15.30 -16.00	***Tea and Coffee***
16.00 – 17.30	d) Optimization of samples for flow-erythroid analysis [M. Loken](USA)
	e) Proposal of an erythroid diagnostic score: pre-work of document on dyserythropoiesis [T.M. Westers](NL)
	(Dys)thrombopoiesis: the future in MDS?
	Chair: M. Loken (USA)
	f) Introduction to (dys)thrombopoiesis [S. Matarraz](E)
19.30 – 22.30	***Dinner Cruise in Amsterdam***

Saturday 27 October 2012

09.00 - 10.30	**Diagnostic flow parameters**
	Chair: A.A. van de Loosdrecht (NL)
	a) Diagnostic markers beyond the four parameters [D. Subira](E)
	b) Flow cytometry in del(5q) [U. Oelschlaegel](G)
	c) Application of the Euro-flow concept in clinical practice [V. Van der Velden](NL)
10.30 - 11.00	***Tea and Coffee break***
11.00 - 12.30	**Application of flow cytometry in MDS**

	Chair: M. Loken (USA)
	a) Role of FC in integrated diagnostics [R. Ireland](UK)
	b) Prognostic scoring [C. Alhan](NL)
	c) Impact of FC post chemotherapy for myeloid neoplasms [S. Chu](Taiwan)
12.30 - 13.30	***Lunch***
13.30 – 14.30	**Predictive value of flow cytometry in MDS treatment**
	Chair: K. Psarra (Gr)
	a) Prediction of response by flow cytometry [A.A. van de Loosdrecht](NL)
	b) The –*labelling index*- of BM subpopulations [S. Matarraz](E)
14.30 – 15.30	**The future of flow cytometry in MDS**
	Chair: W. Kern (G)
	a) Prospective studies: ***the final template*** [W. Kern](G)
	b) Where to go with flow in MDS [M. Loken](USA)
	c) The position of the MDS-Flow working group within ELN:
	How should we further increase our impact? [T de Witte](NL)
	Concluding remarks [A.A. van de Loosdrecht](NL)
	-*Vaarwel*- and close of meeting

Financial disclosures Amsterdam 2012 meeting

An EFS grant **of E 2000,-- was awarded** of the total budget of 16,000.-- Euro. 35 participants mainly from Europe for a 2-day conference with a 2-night stay at the WestCord Fashion Hotel In Amsterdam were invited. 31 participants actually participate the meeting. **The final total costs were: E 14,283.74.**

Curriculum Vitae of Chair: Dr AA 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 and in 2012 professor of hematology at the department of Hematology, VUmc, Amsterdam. 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 130 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. He is Principle Investigator of the first in human use of an allogeneic DC vaccine in AML in a phase-I study (DCone in AML; DCprime). 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 with a recently defined collaboration with Dr. S. Kordasti and prof.dr. G. Mufti at King's in London. 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, established a firm collaboration with dr. M. Loken and dr. D. Wells, at HematoLogics Inc, Seattle, USA, and initiated a platform (chair of ELN WP8/flow WG) within the ELN on the

implementation of flowcytometry in MDS in Europe. Finally, he is chair of the Data Base Sharing Committee (DBSC) of the International Working Group on prognostic markers in MDS (IWG-PM) of the MDS Foundation Inc.

Final ELN Participants list (35; 31 attended: X: could not attend finally)

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