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"Old tricks and new procedures" – a report from the 34th Annual Meeting of the European Group for Blood and Marrow Transplantation EBMT, March 30 – April 2, 2008, Florence, Italy

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The European Group for Blood Marrow Transplantation held its 34th annual meeting between 30th March and 2nd April 2008 in Florence, Italy. Over 4700 participants engaged in lively discussions focussed on all aspects of haematological stem cell transplantation from basic science up to nursing issues. While the optimal incorporation of novel drugs, targeted therapies, stem cell engineering and up-to-date molecular wizardry into classical transplantation regimes was intensively debated some seemingly long forgotten issues resurfaced, not half as boring as thought of. All scientific contributions to the meeting are available as a supplement to *Bone Marrow Transplantation*[1] to which all following reference numbers are alluding. The authors will present a strictly subjective selection out of the 1364 abstracts.

Keywords: BMT, predictive models, auto-immune diseases, AML, myeloma, transplantation complications

Basic science

Avigdor et al. (# 100) brilliantly outlined the complex regulation by which progenitor cell egress during stem cell mobilisation is facilitated via an inversely G-CSF driven feedback loop on MT1-MMP and RECK expression on progenitors, resulting in a net increase in MT1-MMP activity. MT1-MMP-driven proteolysis of CD44 then diminishes adhesion to marrow components, leading to progenitor cell egress. This autonomous cellular mechanism could putatively be exploited to improve mobilisation procedures in the future.

The matching status of KIR (killer immunoglobulin receptor) – ligand in unrelated cord blood stem cell transplantations performed for acute leukaemia was analyzed in 218 pts. by Willemze et al. (# 83). The use of KIR-ligand alloreactive donors compared to non-reactive ones resulted in a lower relapse incidence at 2 years post HSCT (p 0.03) and increased DFS and OS, especially in AML pts. Thus, mismatching for inhibitory KIR-ligands in GvH direction could become a major criterion in donor selection. This analysis was given the prestigious *Van Bekkum award*.

Themeli et al. (# O104) shed new light on the understanding of epithelial tumourigenesis in the context of chronic GvHD. Their *in-vivo* and *in-vitro* data clearly demonstrated the induction of genomic instability by alloantigenic reactions potentially predisposing pts. to secondary neoplasia.

Prognostic factors, predictive factors and scoring systems

While genomic, transcriptomic- or proteomic-based candidates for prognostic or predictive biomarkers are numerous and evermore widely discussed, laborious retrospective analysis of huge numbers of pts. can result in simple scoring tools with astonishing predictive power as was demonstrated by Gratwohl et al. (# O105) in their talk on the further refinement of the EBMT risk score for outcome prediction (Tab. 1) respective to allogeneic HSCT. TRM improved significantly over time (RR 1980–89 1.0; 1990–99 0.71; since 2000 0.50) Absolute TRM rates declined less markedly due to a shift towards higher risk pts., being transplanted in more recent years. With over 50,000 (!) transplant procedures analyzed, the resulting score separated distinct risk categories in all diseases, for all donor types, for all stem cell sources and for pts. with reduced and standard conditioning. The EBMT score is likely to be refined by including further parameters (e.g. CMV Status). With the help of the EBMT score, risk categories can be clearly defined and integrated into risk assessment algorithms to be used as decision tools in clinical situations, where both transplant and non-transplant treatment options are available.

Other scoring systems were presented for the evaluation of the influence of comorbidities on reduced intensity allografting for lymphoma or myeloma (# O388), the outcome of allogeneic HSCT in OMF (# P982), auto/allo procedures in

[1]BMT 41 (Suppl 1): S1–466, 2008.

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Tab. 1: The EBMT risk score for outcome prediction in allogeneic HSCT (Updated Gratwohl et al. 2008)

	Score 0	Score 1	Score 2
Stage of disease	Early	Intermediate	Advanced
Age of pt.	<20 y	20–40 y	>40 y
Time from diagnosis to transplantation	<1 y	Over 1 y	
Histocompatibility	HLA-id Sibling	Other	
Donor/recipient sex match		Female donor-male recipient	
Transplant related mortality at 5 years Score 0 15.4% Score 1 22.1% Score 2 27.6% Score 3 32.4% Score 4 37.9% Score 5 42.6% Score 6/7 49.7%			
Procedures with an EBMT score of 5 or more are generally not recommended			

myeloma (# P665), autologous HSCT in myeloma (# P666, # P668) as well as the outcome of allogeneic HSCT in t-MDS and t-AML (# P743).

Auto-immune diseases (AIDs)

The depletion of the autoreactive immunological memory (immuno-ablation) followed by autologous haematological stem cell therapy based on ATG-centered conditioning regimes offers hope for achieving durable long-term remissions in pts. with a variety of refractory AIDs as different as systemic lupus erythematosus [SLE] (# O103, # P553, # 122), multiple sclerosis of the relapsing/remitting clinical subtype [MS] (# 120), severe systemic sclerosis [SSc] (# 121, # O155) and paediatric auto–immune disease (# 124a, # 124b). The reactivation of thymic education and re-induction of self-tolerance has been experimentally proven in responders (Alexander et al. # O103) and the concept of immuno-ablation and resetting of the *Immunostat* has now entered the developmental stage of large controlled randomized clinical phase II trials like ASTIMS for MS, ASTIS for SSc, and ASTIL for SLE, or the implementation of registries for paediatric indications.

For all the mentioned studies, promising interim analyses were demonstrated. Each of them held the potential to clarify the definite therapeutic value of the concept of imuno-ablation in different AIDs in the years to come.

Chronic leukaemia, PNH, and lymphoma

Is there still a role for allogeneic transplant in CML in times of TKI-based therapies? At least in carefully selected pts., the option of the therapeutic approach offering the only known definitive cure for the disease should not be too easily discarded. Helm et al. (# 241) demonstrated a probability of survival of 88% at 5 years (LFS 61%) in a competitive risk model developed by analysing 214 low risk pts. with an EBMT score of 0-, 1- or 2 transplanted after Imatinib failure, thus proving that allogeneic transplantation remains a valid therapeutic option for such pts.

A similar controversy is going on concerning the management of paroxysmal nocturnal haemoglobulinuria (PNH) in times of Eculizumab. The Italian GITMO study group presented 19-year data regarding matched sibling transplantation (# O158) in PNH with a favourable 10-year DFS of 70% but a 6-month TRM of 34%. Risitano et al. (# P569) in contrast evaluated the pros and cons of long-term complement inhibitor therapy with Eculizumab, proving to be very efficient in most pts., but complicated by extravascular haemolysis or aplastic features, necessitating the use of erythropoetins, or additional immunosuppression in some pts., and life-long extremely costly drug application in all of them. Lacking any randomized comparisons of this options an individualized appraisal taking into account disease severity, patient preferences and the EBMT score should be applied.

The sessions on lymphomas mainly focused on the integration of novel drugs like Bortezomib (# P821) or concepts like radio-immunotherapy [RIC] (# P835; # O263) into conditioning or consolidation regimens in both high-risk allo- and auto settings. Allo-RIC might also be an option in selected pts. with advanced 17p-CLL with an estimated DFS of 38% and an OS of 47% at 4 years as illustrated by Schetelig et al. (# O282) in 56 pts.

The role of PET scans as predictive examination or therapy steering instrument is still unsolved and probably prone to be diverse in different clinical scenarios e.g. positive correlation in DLBCL treatment (# P827) and no correlation at all respective to Hodgkins disease response prediction in another series (# P837).

Multiple myeloma

Three main topics dominated the, not so few, myeloma sessions

Incorporation of "novel agents" (Bortezomib, Revlimid, and Thalidomid) into myeloma therapy, especially as part of alternative conditioning, induction (# P671), consolidation (# P675; # P669), maintenance or post-relapse (# 238) treatment schedules.

The unsolved question of the role of reduced intensity (RIC) allogeneic transplantation in myeloma, be it in the auto/allo (# O377), allo-upfront (# O380) or the context of randomized comparisons (# 246; # O373). While neither the PETHEMA study (# O373) nor the interim analysis of the EBMT study (# 246), up to now, shows any significant difference in DFS or OS comparing allogeneic to non-allo treatment concepts, both nevertheless implicate the existence of a plateau in the arm with allogeneic-reduced intensity-conditioning transplantation. Probably, the real challenge we have to solve concerning treatment allocation is rational patient selection. Another astonishing difference in outcome was analyzed by Rosiñol (# O374) comparing *primary progressive myeloma* (PPMM) with first line *non-responding/non-progressive* (NRNPMM) *myelomas* usually often subsumed under the term *refractoy MM*, but under closer scrutiny being applied showing quite diverse clinical courses. While prognosis of PPMM was dismal even after the application of a subse-

quent autologous HSCT, results of NRNPMM pts. nearly approached the ones achieved in transplanted first line therapy responders. As a consequence, pts. with PPMM should be treated inside innovative clinical trials.

The use of early response/relapse indicators like serum-free light chain assay (# 674) or IgH PCR-based approaches (# P661) proved to proceed frank relapse often for over one year was another focus of interest, potentially being useful to direct early immunological interventions like DLI (# P1030) post-transplantation.

Acute leukaemia, MDS, stem cell sources and cellular therapies

The implementation of Imatinib in the treatment algorithms for Phi+ ALL is on one hand clear cut, but on the other hand still unclear concerning its concrete execution, showing promising results both in the pre- and post-transplant setting as illustrated by Wassmann (# O138, # O142). Nevertheless, close response monitoring remains a prerequisite.

In high-risk AML scenarios like FLT3-ITD mutated AML (# O139), AML with complex aberrant karyotypes (# O401) or either of these characteristics (# O142) three groups independently demonstrated promising results for very early treatment intensification by allogeneic approaches, questioning more traditional induction/consolidation schemes. With regard to relapsing or refractory acute leukaemia regimens containing Clofarabin (# P732, # P525) were intensively discussed.

Two *old fashioned* issues re-emerged in several acute leukaemia sessions with quite unsuspected results presented. Gorin et al. (# O145) reported an adverse outcome, especially concerning relapse incidence, in an analysis of over 7000 autologous transplantations for AML comparing peripheral blood (PB) with bone marrow (BM) as a source of stem cells (p 0.003); this was corroborated by Nachbaur et al. (# P573) showing no benefit for the use of PB vs. BM in a single centre allogeneic transplantation series either. So, may be we stopped classical BMT in early eighties too early and should rethink the institution of randomized trials on the subject. The same holds true for autologous HSCT for AML as a therapeutic principle of its own right, proven to be quite efficient at least in good or standard risk pts. in several analyses (# P493, # 195, # O141 – [here again BM outperformed PB-based procedures]). For example, in rapid remitting core-binding factor leukaemias an LFS of –70% at 3 years is feasible with autologous HSCT alone. So, once again a therapeutic option, nowadays underused, might merit some re-evaluation, perhaps even more in innovative concepts combining autologous HSCT with post-remission MRD-targeted approaches.

In MDS a promising strategy of 5-AZA induction in IPSS INT-2 and high risk MDS as well as t-AML were introduced by McCarthy et al. (# P746) in a pilot study, in which the 5-AZA induced pts. outperformed historical controls, by a mile, leading to the institution of a large multicenter trial in the US by now.

With regard to alternative cellular therapies, interesting data on direct bone infusion of matched unrelated cord blood (# O164), or much superior outcome of co-transplantation of mesenchymal stem cells with a single unit of cord blood compared to double cord blood transplantation (# O146) in adults were presented. These results could lead to a simplification concerning cord blood access and availability.

The unmet need of optimisation of haplo-identical transplantation might be met by concepts like (# O290) T-cell depleted, allografting supplemented with an add-back of genetically modified T-cells (e.g. with HSV-thymidinkinase), transplantation.

Quality of life and late effects

The issues of sexual dysfunction in long-term survivors of BMT were discussed in general (# O132) and under the specific issue of the female pt. with cGvHD (# O370). Both investigations proved a high prevalence of sexual disturbances post-BMT and argue for increased problem awareness inside routine follow-up of pts. and more frequent institution of specific interventions reaching from counselling as far as the application of Tacrolimus cream. Appearance and severity of chronic GvHD are furthermore highly significantly correlated to reductions in the quality of life as illustrated by a prospective multicenter evaluation (# P421). An increased risk for cardiovascular events in survivors of BMT was demonstrated by Tichelli et al. (# 200) approaching 6% at 15 years (and 17% in pts. with additional cardiovascular risk factors) highlighting the necessity of physician alertness for such complications and the exigency of combating additional risk factors in transplanted pts. (e.g. optimizing blood pressure, non-smoking ,…).

Iron overload (IO)

Iron overload was discussed in quite a broad spectrum of clinical question sometimes with surprising results. Kaloyannidis et al. (# O402) pinpointed to a reduced relapse incidence for myeloid malignancies in pts. successfully chelated with desferrioxamine post-allogeneic HSCT towards ferritin levels <2000 ng/ml ($p = 0.04$) in a retrospective analysis. The effect proved to be stable after multivariate analysis, thus meriting prospective studies. Lower ferritin also correlated to less transplantation complications in children (# P431) with a cut-off of ferritin 1000 ng/ml, and pts. transplanted for aplastic anaemia (# P566), as well as with the development of post-transplant metabolic syndromes (# P439). With superconducting quantum interference a new non-invasive accurate tool for measuring IO was described (# O390).

Infectious complications and infection prohylaxis

A systematic review and meta-analysis of all published controlled randomized clinical trials on immunoglobulin prophylaxis with either pooled or CMV-hyperimmune IVIG in pts. undergoing allogeneic HSCT failed to prove any clinical benefit concerning survival for this costly intervention (# O267) but alluded to an increase in adverse effects and VOD. The authors concluded that current evidence does not support the use of IVIG or CMV-IVIG post-HSCT.

A retrospective EBMT survey (# O365) as well as several cases (e.g. # P928) argued for the existence of a therapeutic effect of cidofovir on BK-Virus associated haemorrhagic cystitis after HSCT, thus postulating the urgency of prospective stud-

ies of the issue. In a randomized study, Volin et al. (# O268) proved equal efficiency of p.o. and i.v. pre-emptive therapy for CMV-infection after HSCT.

The complex interactions of modern immunosuppressants and antimycotics were widely discussed (# P916, # P889) spotlighting the necessary caution needed for combining these innovative drugs. Although old fashioned interventions like amphotericin B inhalative prophylaxis might be efficient in certain clinical settings (# P894), the over-all usefulness of modern antimycotic drugs was proven by a significant reduction in deaths with their respective institution by Auberger et al. (# P874) in large single center longitudinal evaluation as well as in an elegant health economic evaluation of fluconazol vs. posaconazol prophylaxis in GvHD pts. in the Netherlands demonstrating a cost-effectiveness at 50,000 EU/QALY in this high risk group of pts.

Miscellaneous

An indicative light on our communication skills was shed by Caocci et al. (# O185) analyzing physician and patient perceptions to be strongly discrepant for the risks of developing GvHD or dying from complications of an unrelated allo-transplant after extensive consent seeking communication.

Another highly self-educative presentation was made by Szydlo et al. (# P1087), demonstrating on the example of a presumed interference of the zodiac on transplant mortality for CML how easily statistics can be manipulated to deliver a seemingly important result on any pseudoscientific parameter by "applying inadequate or inappropriate statistical analyses when rational scientific discourse has become impotent". A conclusion that is obviously valid not only in transplant related matters.