BSBMT NEWS

British Society of Blood and Marrow Transplantation

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BSBMT Scientific Day

Harnessing the Immune System to Fight Cancer

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INSIDE...

Well an aeon has passed since we last all met here within the hallowed pages of the BSBMT newsletter and the world has turned on its axis in that time. Although we now live in a post-truth world, you can rest easy in the knowledge that this publication remains a haven from the horrors so readily to be found in the rest of the world's press. You won't find articles here on the impact of Brexit on stem cell transplantation, nor have I canvassed Donald Trump's views on T cell depletion. What you will find within our convivial pages is **Rubeta Matin's** excellent guide to cutaneous GvHD, refreshingly and importantly told from the view of a dermatologist who sits alongside our haematology brethren in a transplant clinic and helps them to differentiate between keratosis pilaris and icthyosis when the going gets tough and the rashes are erupting thick and fast. Prepare your CPD login – this article is worth a point in anyone's portfolio.

David Tucker and **Simon Rule** (fresh from his triumphant ASH education session) are here to update us on the role of SCT in the management of mantle cell lymphoma.

The educational activities of the BSBMT roll on too and I provide reports of the **Education** and **Scientific** days for those of you who were unable to make it.

Finally there is a welcome message from the new BSBMT President, Dr Jenny Byrne.

And so onwards...

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BSBMT

BSBMT Scientific Day

Some years ago now, when the world was younger and the prospect of Donald J Trump as President of the United States of America seemed laughable, I was a medical student. During the course of my time pursing this occupation I was required to write an oncology dissertation on a developing area of oncology. As the tutor went around the room asking for our potential titles, student after student announced that they were going to dissert, pontificate and otherwise hold forth on the topic of angiogenesis inhibitors. I was last to put forward my title and, laughing down from lazy eyelids and flicking a speck of dust from the irreproachable Mechlin lace at my wrists, I announced that my dissertation was to be on the topic of tyrosine kinase inhibitors. On the basis of this anecdote I would like to make some claim to prescience, for 'where art though now oh avastin!' I hear you cry and 'buried under a dashed pile of drugs whose names end in –inib' comes back the answer from poor old avastin.

However, before I become over-ebullient at my foresight, I must recall that during this same oncology attachment I was much enamoured of the prospect of immunotherapy for cancer, until a kindly lecturer pointed out that people had been trying to get the immune system to kill cancer cells for years and the bally thing didn't work and didn't ever look like it was going to work.

So, shamefully, I turned my back on cancer immunotherapy and eventually took up the only form of it that did seem to work—namely allogeneic stem cell transplant.

On the basis of this anecdote and, after hearing the material presented at the annual scientific day, I must retract my claim to prescience. It's 2016 and immunotherapy has kicked in the doors of oncology and is currently asking cytotoxic chemotherapy if it would like to step outside and sort things out man-to-man.

Dr Sergio Quezada

Immune checkpoint inhibitors – the theory

The meeting opened with a scientific tour de force from **Dr Sergio Quezada** of the UCL Cancer Institute. He began by re-capping the more that 100-year history of cancer immunotherapy. Whilst it has been known for some time that T cell activation requires a signal from antigen presented on MHC *together* with a second co-stimulatory signal from a molecule such as B7, in the case of cytotoxic responses against tumour cells this hasn't been enough; despite appropriate antigen and co-stimulation, cancer cells seem to be able to prevent cytotoxic cells from mounting an attack on them. The tide began to turn with the discovery and cloning of the so-called checkpoint inhibitory molecules and their ligands. The first of these was CTLA-4. CTLA-4 normally resides in vesicles within the T cell. However, when the T cell binds antigen via the T cell receptor and CD28 on the T cell surface binds B7 on the antigen presenting cell, CTLA-4 migrates to the cell surface where it competes with CD28 for B7 binding and thus acts to switch off the T cell activating signal.

In mouse models of melanoma tumours are infiltrated by numerous regulatory T cells (Treg), which supress the immune response, but relatively few effector cytotoxic T cells (Teff), which can act to attack tumour cells. Mice vaccinated with a tumour vaccine, together with a CTLA-4 blocking antibody show a significant decrease in the number of Treg in the tumour but not in the draining lymph node. This decrease in Treg in the tumour is due to antibody-dependent cellular cytotoxicity (ADCC) mediated by the CTLA-4 antibody directed against tumour-infiltrating Treg, which strongly express CTLA-4 (unlike the Teff in the tumour); the greater the ability of anti-CTLA-4 to activate ADCC, the greater the reduction in Treg within the tumour and the larger the amount of tumour regression observed in the mouse model.

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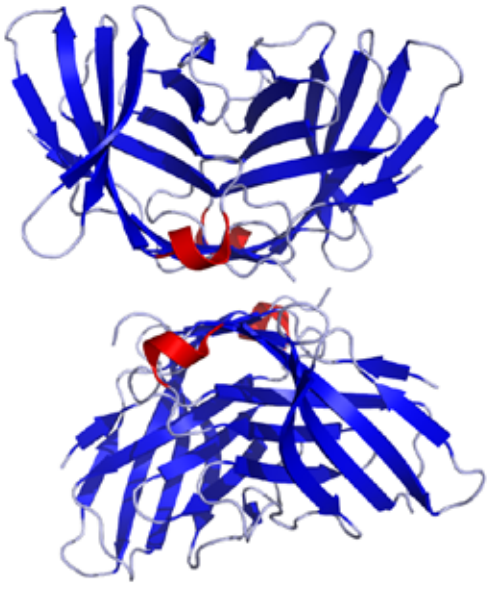
Dr Quezada then turned his attention the antigens stimulating tumour immune responses in the first place. There are data to suggest that the more mutations a tumour possesses and therefore the more potential neoantigens it may express, the more likely it is to respond to CTLA-4 blockade with ipilimumab. Some of these mutations may be founding mutations expressed by all cells in the tumour (so-called 'trunk' mutations), whilst others may only be expressed by certain sub-clones within the tumour (branch mutations). In non-small cell lung cancer immune responses directed against trunk neoantigens are more important in achieving effective anti-tumour immune responses than those against branch mutations. This makes sense as, if you are trying to cut down a tree, you do so at the trunk and not at the branches. In the light of this then it may be that the use of genomics to identify trunk neoantigens and develop vaccines against them comes to play an important part in the treatment of cancer through a vaccination/immune checkpoint blockade approach.



The crystal structure of CTLA-4

By Ramin Herati [Public domain], via Wikimedia Commons

Dr James Larkin

Immune checkpoint inhibitors – the practice

Dr James Larkin from the Royal Marsden Hospital presented the medical oncology perspective of immune checkpoint inhibition. Malignant melanoma is a tumour that is effectively insensitive to chemotherapy and therefore has been a focus for the development of immune therapies for some time. Ipilimumab was the first checkpoint inhibitor to be trialled in this disease and has been demonstrated to double the five-year overall survival in metastatic melanoma from approximately 10 to approximately 20%. The PD-1 inhibitor nivolumab is more effective than ipilimumab and the combination of the two as assessed in the checkmate 067 study may be better again (although the study was not powered to identify this difference).

The downside to allowing unfettered immune system activation is some quite significant inflammatory/ autoimmune toxicity. It was common to stop treatment in the first 12 weeks of the checkmate study due to toxicity, with 20% grade 3-4 toxicities reported for the single agent ipilimumab arm and a high rate for the combination arm. Frequent toxicities include colitis, transaminitis, pneumonitis, encephalitis, Guillain-Barré syndrome and pituitary failure. Whilst these toxicities seem to have caused some anxiety in the medical oncology world, the prospect of a massive inflammatory immunological attack on multiple organs and tissues which requires treatment with high doses of steroids and strong optimism, left the bone marrow transplanters in the room feeling like they were on much firmer ground. The combination of ipilimumab and nivolumab for melanoma treatment has now been approved by the FDA - meaning that the prospect of the clinical toxicity of this treatment may pale into insignificance when we consider the financial toxicity of this combination.

After two talks firmly rooted in oncology the audience was ready to move on to the application of these treatments to the world of haematological malignancy.

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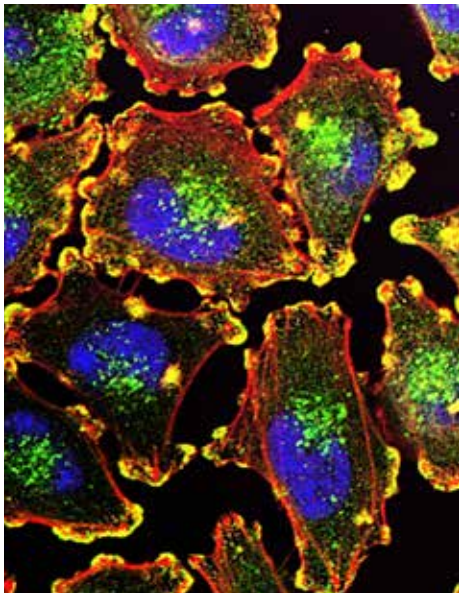

Metastatic melanoma cells

By Julio C. Valencia - This image was released by the National Cancer Institute, an agency part of the National Institutes of Health, with the ID 9872.

https://commons.wikimedia.org/w/index.php?curid=39782976

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Dr Matthew Davids

Immune checkpoint inhibition after allo-SCT

Dr Matthew Davids (Dana Faber Cancer Institute, Boston) came to our aid presenting the first results of his study of the use of immune checkpoint blockade following allo-SCT. Clearly in a group of patients who are already at risk of a significant allo-immune inflammatory reaction in the form of GvHD, the safety implications of immune checkpoint blockade in this situation are paramount.

In an initial study doses of ipilimumab of up to 3mg/Kg did not induce GvHD, although did result in grades 2-4 organ-specific immune adverse events in 4 of 29 patients. Disease responses were modest, but tumour regression was observed in 3 patients with lymphoid malignancies. A subsequent larger study has included patients with a wide range of haematological malignancies who relapsed at least 3 months post allo-SCT, who had >20% donor T cell chimerism and measurable disease without active extensive cGvHD and who were off immunosuppression.

In 28 patients receiving 3mg/Kg there was 1 episode of grade 3 liver GvHD and 1 clinical response. In 22 patients receiving 10mg/Kg there were 3 cases of GvHD and 4 immune related adverse events. The overall response rate was 35% with a 25% CR rate. The response rate appeared to be particularly good for extra-medullary disease with 3 responses observed in patients with AML that had relapsed as leukaemia cutis. The one year OS of this study was 50% but PFS was <20%. Patients whose disease responded to immune checkpoint blockade had significantly fewer Treg in the peripheral blood at 8 weeks than was found in the blood of non-responders.


Dr Patrick Johnston

Immunotherapy for lymphoma

While immune checkpoint blockade is in its infancy in myeloid malignancies, it is rather further advanced in the lymphoma world. Lymphoma and stem cell transplant most frequently encounter each other under the aegis of the autologous SCT for relapsed NHL.

Dr Patrick Johnston (Mayo Clinic) began by taking us back to the PARMA trial – the original pivotal study that established ASCT as the treatment for relapsed high grade NHL. The benefits of ASCT in the rituximab era are much less clear, as the data from the CORAL study demonstrate. Studies of the tumour microenvironment in lymphoma indicate that lymphoma cells may be able to recruit regulatory T cells to the tumour by secretion of CCL22, thus there is a rationale for immune checkpoint blockade in this disease.

The anti PD-1 antibody pidilizumab, when administered following ASCT for DLBCL in a phase II trial was associated with a PFS of 72% at 16 months and an impressive 70% in those patients who had persistent PET-avid disease after salvage chemotherapy (Armand J *et al* 2013 *J Clin Oncol* **31** 4199). Although there was no comparator arm in this study, the data presented are relatively immature and the indications for ASCT are heterogeneous, these outcomes compare favourably with those of the CORAL study where 3 year EFS for patients relapsing after prior rituximab-based therapy was 21%. There are also data demonstrating activity for pidilizumab in follicular NHL and nivolumab and pembrolizumab in NHL and Richter's transformation of CLL.

Immune checkpoint inhibition isn't the only immunotherapy game in town of course and CAR-T cells have been causing much excitement of late. Responses to CAR-T cells have been reported in phase I studies in follicular lymphoma and recently their use has been demonstrated as feasible following ASCT for NHL. This is clearly a field where immunotherapy has potential to develop and possibly improve the outcomes of ASCT for NHL in the rituximab era.

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Dr Charles Crawley's presentation to outgoing head of the BSBMT registry, Keiren Kirkland

BSBMT open meeting

The scientific element then took a back seat as the BSBMT business meeting took to the stage. The most significant event to report from this section is that the BSBMT said goodbye and happy retirement to **Keiren Kirkland** who has been head of the BSBMT registry since 2001. Tributes came from the great and the good demonstrating the great affection which Keiren is held in by all who have worked with her.

In the afternoon the now familiar abstract competition took place where the scientific abstract prize was won by Dr Paul Maciocia (UCL) and clinical prize by Dr Paul Ferguson (Queen Elizabeth Hospital Birmingham).

MRD in AML

The day was then completed with a look at MRD in AML presented by **Dr Sylvie Freeman** (University of Birmingham). MRD has been long established in the ALL firmament as a central predictor of outcome to therapy. With multiple lines of attack on the same problem in AML progress is beginning to be made. Dr Freeman was interested not only in the question of what MRD tells us about management of AML, but also what it has to say on the biology of relapse. Dr Freeman commented that next generation sequencing of AML genomes has not yet solved the question of risk assessment in this disease as clonal complexity, epigenetic factors and the tempo of clonal evolution determine relapse. Although we are all familiar with the concept of morphological remission as the goal of induction chemotherapy, several studies have now shown that its predictive power is trumped by MRD. Interestingly CR with incomplete count recovery (CRi) also appears to be a poor prognostic group irrespective of whether it is MRD positive or negative, leaving full, MRD negative, CR as the only good prognostic group following AML induction.

For some time it was hoped that the WT1 antigen might represent a route to a near universal MRD marker in AML as it is overexpressed in a majority of cases of the disease. However, its expression at follow up proves not to be stable making it an unreliable marker. Molecular markers can be of immense value when there is a single universal translocation or mutation available to monitor, as David Grimwade's work on NPM1 demonstrates. Where present there is no marker yet described more sensitive than NPM1. Next generation sequencing may have a role to play in genes with multiple described mutations for example RUNX1 for which there are more than 200 mutations reported in AML.

Dr Freeman's main research interest is in immunophenotyping for MRD detection in AML. The presence of a leukaemia aberrant immunophenotype (LAIP) post course 1 is predictive of outcome in all risk groups of AML. In standard risk disease this marker, like NPM1, is most predictive post course 2 chemotherapy. The LMPP precursor population of marrow may well represent a surrogate for the leukaemic stem cell (LSC) fraction within marrow. Therefore gating on this group may be a way of improving sensitivity of flow over immunophenotyping of the bulk population. Standardisation methodology through the EuroFlow group will help to expand comparable data between groups in the field and the development of a single tube for LSC detection at diagnosis is underway. Lastly emerging data from the FIGARO trial on what happens to MRD following allo-SCT are starting to look very interesting and we will need to examine these data in detail when they are mature.

Thus another fascinating scientific day drew to a close. Thanks must go to the organisers – Professors Ronjon Chakraverty and Persis Amrolia for another great programme.

TRANSPLANTATION IN MANTLE CELL LYMPHOMA

D. L. Tucker, S. A. Rule

David Tucker

Simon Rule

Summary

Twenty years after it was established as a unique clinical entity, mantle cell lymphoma (MCL) continues to pose a considerable challenge to clinicians. It is generally an aggressive and incurable form of NHL, typically presenting at a late stage, often with extranodal involvement and preponderance for older males. The natural history of MCL varies: therapy is usually indicated at presentation but there also exists a small, distinct, indolent subtype, often with circulating disease and spleen involvement which can benefit from a watch and wait approach.

It is broadly accepted that front-line therapy incorporating high-dose cytarabine and rituximab followed by autologous transplantation in first remission provides the deepest and most durable response for younger, fitter patients. Allogeneic transplantation is generally not recommended first-line but should be considered at first relapse in those who are eligible. The era of targeted molecular therapy has delivered several new drugs with proven efficacy together with modest side effect profiles as single agents. The sequencing and combination use for these new drugs is in its infancy, but they offer an opportunity to become integrated into and potentially improve stem-cell transplantation strategies.

Key Points

Autologous SCT in first remission remains the consolidative treatment of choice for those fit enough. There have not been any trials comparing ASCT with alternative maintenance strategies.

MCL is a heterogenous disease with distinct molecular and genetic variation. This may lead to a risk adapted approach in future, but more evidence from clinical studies is currently required to support this.

Allogeneic transplantation is considered effective in MCL with good evidence for a GVL-effect but lack of quality comparative trials with autologous SCT and an increased TRM risk restrict its application to the relapse setting, outside of clinical trials.

Targeted molecular therapies already show impressive efficacy in MCL but remain to be tested in combination with transplantation. However their use as a bridge to transplantation offers efficacy with the advantage of limited toxicity.

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Mantle Cell Lymphoma - A Heterogenous Disease and an Evolving Therapeutic Landscape

In the last decade there have been significant advances in both our understanding of MCL as a lymphoma subtype and the therapeutic options available for patients. The heterogeneity of MCL is becoming better characterised with the identification of a complex variation in genetic and molecular biology. [1–3] Front-line treatment with combinations of immunochemotherapy and consolidation methods have been refined to improve remission quality and duration whilst minimising toxicity and several new molecular therapies, targeted at various signalling pathways within the lymphoma cell, have been identified, studied and licensed for therapeutic use. [4,5] As a consequence, survival outcomes have improved. For younger, fitter patients, an intensive induction regimen consolidated in first remission with an autologous transplant (ASCT) can induce a durable disease-free remission and a median overall survival of approximately 7 years. [6–8]

The growing number of new therapeutic options has already altered the way MCL is treated in the relapse/refractory setting and promises further change in the realm of transplantation as these drugs are sequenced and combined with established therapies. [9] With this evolution of MCL therapy, several important questions arise: what does auto-SCT add to chemotherapy in the era of rituximab and targeted molecular therapies; what is the role for allogeneic stem-cell transplantation (allo-SCT) in the era of novel agents and what strategies can be employed at relapse?

The Role of Autologous Transplant for MCL in the Rituximab Era

For younger, fitter patients, a cytarabine/rituximab-based (R-HiDAC) induction regimen followed by autologous transplantation in first remission is considered the standard of care in MCL. [4,10,11] However, given the median age at diagnosis is 68yrs, individuals are often at the cusp of or beyond eligibility for an intensive approach. For this group, there has been an improvement in survival over the last few years due to the widespread adoption of rituximab into treatment regimens and general improvements in supportive care.

In 2009, Hoster et al. demonstrated that the addition of ASCT to a CHOP induction regimen led to longer progression-free and overall survival in responding patients compared with CHOP and maintenance therapy with interferon-alpha. [6] Since then CHOP has been superseded by induction regimens incorporating cytarabine and rituximab and the need for ASCT in this setting is not known but widely adopted. The European mantle cell lymphoma study for younger patients found little benefit from auto-SCT in increasing the proportion of MRD-negative patients after an R-cytarabine-containing induction regimen. [12] The R-HyperCVAD regimen produces excellent responses as front line therapy for MCL without an ASCT consolidation. [13,14] This is a particularly dose-intensive approach and these results have not been reproduced by several similar multicentre studies. [15,16] Consequently this particular alternative regimen is generally regarded as too toxic for most patients.

The best results observed in a multicentre setting come from the Nordic Lymphoma Group where 160 patients under 66yrs were treated with three cycles of R-CHOP alternating with 3 cycles of R-DHAP prior to ASCT for responders. Overall and complete responses were seen in 96% and 54% respectively with a 6 year OS of 70% and an NRM of 5%. [7] This study represents the strongest supportive evidence for an induction regimen incorporating rituximab and high-dose cytarabine followed by ASCT in first remission. A summary of other important trials is shown in Table 1 on page 8.

The addition of maintenance rituximab to a schedule of R-CHOP chemotherapy has been shown to confer a progression-free but not overall survival (OS) advantage in older patients with MCL. [17] The use of maintenance rituximab following ASCT has also recently been studied. Perhaps unsurprisingly, an interim analysis presented at ASH 2014 demonstrated an improvement in EFS and PFS in the maintenance arm, although an OS advantage is yet to be observed. [18] Based on the immaturity of these data, maintenance rituximab following ASCT is currently not standard practice in MCL.

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Table 1. Recent clinical studies of intensive induction therapy and ASCT in MCL4

Phase	Induction	Consolidation	N	OR (CR) %	Median Response	Median OS	TRM	Reference
II (Single Centre)	R-Hyper-CVAD	-	97	97 (87)	48% 8yr FFS	56% 8yr	8%	Romaguera [14]
II (Multi-Centre)	R-Hyper-CVAD	-	60	83 (72)	61% 5yr PFS	73% 5yr	6.5%	Merli [16]
II (Multi-Centre)	R-Hyper-CVAD	-	49	86 (55)	4.8yr PFS	6.8yr	2%	Bernstein [15]
III (Randomised)	R-CHOP v. R-CHOP/ R-DHAP	Dexa BEAM ASCT ASCT	455	98 (63) v. 99 (61)	3.8yr PFS v. 7.3yr PFS	6.8yr v. NR	4%	Hermine [12]
II (Multi-Centre)	R-Maxi-CHOP + HD AraC	ASCT	160	96 (54)	7.4yr EFS	70% 6yr	5%	Geisler [7]
II (Multi-Centre)	RCHOP / RDHAP	ASCT	60	82 (78)	7yr EFS	75% 5yr	1.50%	Delarue [19]
II (Multi-Centre)	R-CHOP + MTX + HD AraC + Etoposide	ASCT	77	88 (69)	56% 5yr PFS	64% 5yr	3%	Damon [20]
II (Multi-Centre)	R-CHOP + HD AraC	ASCT	87	70 (64)	36% 4yr PFS	66% 4yr	5%	Van't Veer [21]

MCL is a Heterogenous Disease with Distinct Molecular and Genetic Variation: More Evidence to Support a Risk Adapted Approach to Therapy is Currently Required

Current accepted indications for treatment in MCL include: symptomatic disease, progressive disease and disease-associated marrow-impairment or organ dysfunction. [22] However it is now becoming clearer that MCL is a genetically and biologically heterogenous disease with the emergence of genetically and immunophenotypically distinct subtypes. These are characterised clinically by an indolent form, often with circulating disease and splenic infiltration, which may not require treatment for many years and a more common, aggressive phenotype usually requiring treatment at diagnosis. Several prognostic markers, such as high Ki67, SOX11 expression, lack of IGHV rearrangement and accumulation of additional genetic alterations in genes such as TP53 have been characterised as adverse in MCL. [3,4,23–27] Despite these developments, there is currently insufficient evidence to support a risk-adapted strategy in first-line therapy and prognostic markers cannot currently be used to identify low-risk patients in whom de-escalation of first-line therapy (omission of transplant) could be considered. Equally, although patients with high-risk disease defined by MIPI have an inferior outcome following ASCT, there is insufficient evidence to justify a more intensive approach to consolidation such as an alloSCT in first remission. [10]

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The Autologous Stem-Cell Transplant Procedure: BEAM Conditioning Appears Equally Effective in The Absence of Total Body Irradiation (TBI)

Presently, one of two approaches is commonly employed in transplant conditioning for MCL, BEAM or total-body irradiation (TBI)-based conditioning. Because MCL cell-lines are particularly radio-sensitive, it has been suggested that a TBI-containing regimen might improve outcomes. Data from the EBMT registry presented at ASH 2010 point towards a trend in improved disease-free survival in patients in a PR (but not CR) receiving TBI as conditioning for AHCT [28]. However, a recent large retrospective analysis, performed at a single institution, found no difference in PFS or OS whether TBI or BEAM was used. [29] It would therefore seem reasonable to adopt simpler conditioning regimens which avoid the use of TBI.

Allogeneic Transplantation: Evidence for a GVL-effect exists but Lack of Comparative Data with ASCT and an Increased TRM Risk Restrict its Application.

While induction strategies and ASCT can lead to a durable remission, nearly all patients will ultimately relapse and require further treatment. Allogeneic stem-cell transplant (allo-SCT) remains the sole curative therapeutic option. Direct comparisons between alloSCT and ASCT in MCL are relatively sparse in the literature and those that do exist suffer from heavy selection bias. Outcomes vary and depend on several factors, including conditioning regimen intensity, disease-free interval after ASCT and duration and quality of remission at the time of transplantation. Non-relapse mortality (NRM), even with reduced-intensity conditioning (RIC) remains a significant risk (11% - 82%). Nevertheless, patients who relapse following ASCT, and continue to demonstrate chemo-sensitive disease should be at least considered for RIC alloSCT. With proper patient selection, outcomes for alloSCT for MCL can result in cure rates of between 35% and 65%. AlloSCT in first remission should be reserved for healthy, younger patients who are either unable to mobilise stem-cells or (rarely) exhibit primary chemo-resistant disease. Young, healthy patients with short duration of response from ASCT or those with very high risk features (e.g. p53-deletion, high MIPI) should be considered for alloSCT at time of first relapse. Patients with multiply treated (> 4 lines of therapy), relapsed / refractory disease demonstrate a much higher risk of relapse from alloSCT and a significantly increased TRM risk. [30] A summary of clinical trials in MCL is presented in Table 2 on page 9.

Historically, alloSCT has been limited by the early NRM associated with myeloablative conditioning. Initial reports in MCL demonstrated a 3 yr PFS of 55% but at the expense of a TRM rate approaching 40%. The development of RIC allo-SCT has mitigated some of this risk, allowing it to be offered to a larger number of patients.

AlloSCT is rarely used in first remission, usually being adopted for relapsed / refractory disease when patients have a different disease biology which is typically more refractory to conventional therapy. The earliest prospective study employed hyperCVAD cytoreduction in patients under 65 years followed by alloSCT (from a matched, or single mismatched, related donor), versus an ASCT in those patients where no match could be identified. Twenty-six patients received ASCT and 8 received alloSCT. The 3 year OS was considerably higher in the alloSCT arm (73% vs 48%) suggesting a long-term benefit but at the expense of a 25% NRM in the alloSCT, largely due to GVHD. [13]

A larger retrospective study comparing auto- and alloSCT, spanning nearly 20 years and with considerable heterogeneity in treatment regimens, showed a significantly better 6 year OS and PFS in the R/R setting for alloSCT (53% and 46%) versus ASCT (35% and 10%) but rates were not significantly different in first remission. Interestingly, plateaus were seen in both PFS and OS for the alloSCT group with 9 patients (25%) surviving in long-term CR, supporting the concept of a durable remission from alloSCT in MCL.[31]

Several groups have performed subgroup analysis of patients with MCL transplanted in first remission with alloSCT vs ASCT. Although patient numbers are often small, projected EFS rates are generally similar, around 70% at 3 years and 40 – 50% at 5 years. There is, however, a marked difference in TRM (11% – 53% versus 0 – 29%) in the alloSCT and ASCT groups respectively.

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Table 2. Outcomes in patients undergoing reduced-intensity conditioning allogeneic transplantation for mantle cell lymphoma

Series	N	Med Age	Donor type	Conditioning	Disease status	TRM	PFS	OS
Khouri et al. [34]	18	56.5	78% related 22% unrelated	Flu/Cis/Cytarabine Flu/Cy/Rituximab	Relapsed	11.1%	3yr: 82%	3yr: 85%
Robinson et al. [35]	22	52	-	Varied	Relapsed	2yr: 82%	2yr: 0%	2yr 12.8%
Le Gouill et al. [36]	70	56	53% related 47% unrelated	Varied	Relapsed	2yr: 32%	2yr EFS: 50%	2yr: 53%
Maris et al. [37]	33	53.5	48% related 42% unrelated	Flu/TBI	Relapsed	2yr: 24%	2yr: 60%	2yr: 64%
Gayoso Cruz et al. [38]	21	56	Related	Flu/Mel	Relapsed / 1st remission	3yr: 19.5%	5yr: 80%	5yr: 80%
Kruger et al. [39]	33	59	24% related 76% unrelated	Flu/Treosulfan / Ritux Bu/Cy	Relapsed / 1st remission	24%	5yr: 67%	5yr: 73%
Fenske et al. [40]	88	58	41% related 59% unrelated	Varied	Relapsed	1yr: 17%	5yr: 24%	5yr: 31%
Hamadani et al. [41]	128	54	68% related 32% unrelated	Varied	Chemorefractory	3yr: 43%	3yr: 25%	3yr: 30%
Cook et al. [42]	70	52.2	60% related 40% unrelated	Varied	Rel/Ref	5yr: 21%	5yr: 14%	5yr: 37%
Magnussen et al. [43]	28	51	61% related 39% umbilical cord blood	Flu/TBI + Cy or Bu	Rel/Ref / 1st remission	2yr: 15%	5yr: 34%	5yr: 53%

Therefore either alloSCT or ASCT can be effective when used early in the disease course. However, transplant-related complications, even in the era of reduced-intensity conditioning, make allo-SCT less attractive and it is generally not recommended. [32,33]

Transplantation in the Era of Targeted Molecular Therapies

Recently, several newer agents have become available which exploit different aspects of the lymphoma cell biology and the B cell receptor (BCR) signalling pathway (Figure 1 - page 13). The Bruton's tyrosine kinase inhibitor, ibrutinib is arguably the most advanced and impressive of these in single-agent studies and has already been incorporated into several phase II/III front-line combination studies for patients ineligible for transplant. The notion of targeted molecular therapy replacing bone-marrow transplantation in MCL has been entertained but it is now clear that about one third of MCL cases are refractory to ibrutinib in clinical studies [9] and additional relapses occur on therapy, with a median duration of response of 17.5 months in the single agent, relapsed/refractory setting. [44]

To date there are no data on the incorporation of ibrutinib or other targeted therapies into an intensive, front-line approach involving transplantation, although such studies are planned.

Outside of studies, reports are emerging of the use of targeted therapies in the salvage setting for younger fitter patients who relapse during induction therapy or as a bridge to transplantation. [45] What is attractive about using a BTK inhibitor rather than a conventional salvage regimen in younger patients is the striking lack of significant toxicity which accompanies these agents. This should deliver patients to a transplant in a fitter condition, which will allow more patients to advance to a procedure and may improve outcomes generally.

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Given the potential anxiety around the difficulty in rescuing patients post ibrutinib, it is not yet clear how long one can safely wait before transplantation. However given the median duration of response with ibrutinib is around 15 months the procedure should probably be performed before 12 months of therapy have elapsed.

Transplantation in Relapsed MCL

Patients with relapsed MCL have a poor prognosis and should be considered for intensive re-induction followed by consolidation by transplant where appropriate. However the outcome of ASCT and alloSCT are undoubtedly inferior beyond first remission [31] and to a large extent depend on remission quality [35], which is often poor in the salvage setting.

When patients relapse after an ASCT, alloSCT should be considered. One multicentre experience in this context demonstrated a 2 year EFS and OS of 50% and 53% respectively and 1- and 2- year TRM rates of 22% and 32% respectively, with disease status at transplantation having a direct influence on EFS and OS. [36]

The consensus of opinion is that the use of either form of SCT is reasonable where individual patient circumstances allow and disease status at point of second transplantation is the best predictor of response. [10]

Concluding Remarks

Transplantation, by way of ASCT, remains the consolidation therapy of choice for patients with MCL fit enough to undergo the procedure. However, there is a distinct need for well-controlled randomised trials to compare consolidation with transplant with alternative strategies such as maintenance with immunotherapy. The identification of clearer prognostic markers has differentiated MCL into distinct clinical subtypes and these are likely to be incorporated into a risk-adapted approach in clinical trials in the future. The era of targeted molecular therapies is offering new options to patients and physicians in the relapse and salvage setting and promises to further improve prognosis for patients with MCL as they are incorporated into front-line and sequential use.

References

1. *Jares P, Colomer D, Campo E. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. Nat Rev Cancer. 2007;7:750-762. doi:10.1038/nrc2230.*
2. *Jares P, Colomer D, Campo E. Review series Molecular pathogenesis of mantle cell lymphoma. 2012;122. doi:10.1172/JCI61272.3416.*
3. *Fernàndez V, Salamero O, Espinet B, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. Cancer Res. 2010;70(4):1408-1418. doi:10.1158/0008-5472.CAN-09-3419.*
4. *Campo E, Rule S. Mantle Cell Lymphoma – Evolving Management Strategies Address for correspondence : Professor Simon Rule Professor of Clinical Haematology Plymouth University Peninsula School of Medicine and Dentistry Plymouth UK. 2015. doi:10.1182/blood-2014-05-521898.*
5. *Chen Y, Wang M, Romaguera J. Current regimens and novel agents for mantle cell lymphoma. Br J Haematol. 2014;167(1):3-18. doi:10.1111/bjh.13000.*
6. *Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: Results of a prospective randomized trial of the European . Blood. 2005;105(7):2677-2684. doi:10.1182/blood-2004-10-3883.*
7. *Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: A nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood. 2008;112(7):2687-2693. doi:10.1182/blood-2008-03-147025.*
8. *Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma : a phase 2 study from the Groupe d ' Etude des Lymphomes de l ' Adulte. Blood. 2013;121(1):48-53. doi:10.1182/blood-2011-09-370320.The.*
9. *Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507-516. doi:10.1056/NEJMoa1306220.*
10. *Robinson S, Dreger P, Caballero D, et al. The EBMT/EMCL consensus project on the role of autologous and allogeneic stem cell transplantation in mantle cell lymphoma. Leukemia. 2015;29(2):464-473. doi:10.1038/leu.2014.223.*
11. *Dreyling M, Ferrero S, Hermine O. How to manage mantle cell lymphoma. Leukemia. 2014;28(11):2117-2130. doi:10.1038/leu.2014.171.*
12. *Hermine O, Hoster E, Walewski J. Alternating Courses of 3x CHOP and 3x DHAP Plus Rituximab Followed by a High Dose ARA-C Containing Myeloablative Regimen and Autologous Stem Cell Transplantation (ASCT) Increases Overall Survival When Compared to 6 Courses of CHOP Plus Rituximab Followed . In: ASH Annual Meeting.; 2012:151.*
13. *Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem-cell transplantation: An active regimen for aggressive mantle-cell lymphoma. J Clin Oncol. 1998;16(12):3803-3809.*

Continued on page 12

Continued from page 11

14. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol. 2010;150(1995):200-208. doi:10.1111/j.1365-2141.2010.08228.x.

15. Bernstein SH, Epner E, Unger JM, et al. A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213. Ann Oncol. 2013;24(6):1587-1593. doi:10.1093/annonc/mdt070.

16. Merli F, Luminari S, Ilariucci F, et al. Rituximab plus HyperCVAD alternating with high dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. Br J Haematol. 2012;156(3):346-353. doi:10.1111/j.1365-2141.2011.08958.x.

17. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of Older Patients with Mantle-Cell Lymphoma. N Engl J Med. 2012;367(6):520-531. doi:10.1056/NEJMoa1200920.

18. Le Gouill S, Thieblemont C, Oberic L. Rituximab Maintenance Versus Wait and Watch after Four Courses of R-DHAP Followed By Autologous Stem Cell transplantation in Previously Untreated Young Patients with Mantle Cell Lymphoma: First Interim Analysis of the Phase III Prospective Lyma Trial, a L. In: ASH Annual Meeting.; 2014:623.

19. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation (ASCT) in mantle cell lymphoma (MCL): a phase II study from the GELA. Blood. 2012. doi:10.1182/blood-2011-09-370320.

20. Damon LE, Johnson JL, Niedzwiecki D, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol. 2009;27(36):6101-6108. doi:10.1200/JCO.2009.22.2554.

21. van 't Veer MB, de Jong D, MacKenzie M, et al. High-dose Ara-C and beam with autograft rescue in R-CHOP responsive mantle cell lymphoma patients. Br J Haematol. 2009;144(4):524-530. doi:10.1111/j.1365-2141.2008.07498.x.

22. McKay P, Leach M, Jackson R, Cook G, Rule S. Guidelines for the investigation and management of mantle cell lymphoma. Br J Haematol. 2012;159(4):405-426. doi:10.1111/bjh.12046.

23. Hoster E, Dreyling M, Klapper W, et al. cell lymphoma A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. 2012;111(2):558-565. doi:10.1182/blood-2007-06-095331.

24. Determann O, Hoster E, Ott G, et al. Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: Results from randomized trials of the European MCL Network and the German Low Grade Lymphoma Study Group. Blood. 2008;111(4):2385-2387. doi:10.1182/blood-2007-10-117010.

25. Mozos A, Royo C, Hartmann E, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica. 2009;94(11):1555-1562. doi:10.3324/haematol.2009.010264.

26. Navarro A, Clot G, Royo C, et al. Molecular subsets of mantle cell lymphoma defined by the IGHV mutational status and SOX11 expression have distinct biologic and clinical features. Cancer Res. 2012;72(20):5307-5316. doi:10.1158/0008-5472.CAN-12-1615.

27. Rosenwald A, Wright G, Wiestner A, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell. 2003;3:185-197. doi:10.1016/S1535-6108(03)00028-X.

28. Rubio M, Ariane Boumendil, Luan J. Is There Still a Place for Total Body Irradiation (TBI) In the Conditioning Regimen of Autologous Stem Cell Transplantation In Mantle Cell Lymphoma ?: a Retrospective Study From the Lymphoma Working Party of the EBMT. In: ASH Annual Meeting.; 2010:688.

29. Peterlin P, Leux C, Gastinne T. Is ASCT with TBI superior to ASCT without TBI in mantle cell lymphoma patients? Transplantation. 2012;94(3):295-301.

30. Cohen JB, Burns LJ, Bachanova V. Role of allogeneic stem cell transplantation in mantle cell lymphoma. Eur J Haematol. 2015;94(4):290-297. doi:10.1111/ejh.12442.

31. Tam CS, Bassett R, Ledesma C, et al. Mature results of the MD Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood. 2009;113(18):4144-4152. doi:blood-2008-10-184200 [pii]\n10.1182/blood-2008-10-184200.

32. Kasamon YL, Jones RJ, Diehl LF, et al. Outcomes of autologous and allogeneic blood or marrow transplantation for mantle cell lymphoma. Biol Blood Marrow Transplant. 2005;11(1):39-46. doi:10.1016/j.bbmt.2004.09.007.

33. Laudi N, Arora M, Burns L, et al. Efficacy of high-dose therapy and hematopoietic stem cell transplantation for mantle cell lymphoma. Am J Hematol. 2006;81(7):519-524. doi:10.1002/ajh.20646.

34. Khouri IF, Ming L, Rima M. Nonablative Allogeneic Stem-Cell Transplantation for Advanced/Recurrent Mantle-Cell Lymphoma. J Clin Oncol. 2003;21(23):4407-4412.

35. Russell N, Goldstone AH, Robinson SP, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogenic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group fpr Blood and Bone Marrow Transplantation. Hematology. 2002;100(13):4310-4316. doi:10.1182/blood-2001-11-0107. Reprints.

36. Le Gouill S, Kröger N, Dhedin N, et al. Reduced-intensity conditioning allogeneic stem cell transplantation for relapsed/refractory mantle cell lymphoma: A multicenter experience. Ann Oncol. 2012;23(10):2695-2703. doi:10.1093/annonc/mds054.

37. Maris MB, Sandmaier BM, Storer BE, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood. 2004;104(12):3535-3542. doi:10.1182/blood-2004-06-2275.Supported.

38. Gayoso J, Martino R, Balsalobre P, et al. Long-term results of fludarabine/melphalan as a reduced-intensity conditioning regimen in mantle cell lymphoma: The GELTAMO experience. Ther Adv Hematol. 2011;2(1):5-10. doi:10.1177/2040620710396752.

39. Kruger W, Hirt C, Basara N. Allogeneic stem cell transplantation for mantle cell lymphoma-final report from the prospective trials of the East German Study Group Haematology/ Oncology (OSHO). Ann Hematol. 2014;93(9):1587-1597.

40. Fenske T, Zhang M, Carreras M. Autologous or reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chemotherapy-sensitive mantle-cell lymphoma: analysis of transplantation timing and modality. J Clin Oncol. 2014;32:273-281.

41. Hamadani M, Saber W, Ahn KW, et al. Allogeneic hematopoietic cell transplantation for chemotherapy-unresponsive mantle cell lymphoma: a cohort analysis from the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2013;19(4):625-631. doi:10.1016/j.bbmt.2013.01.009.

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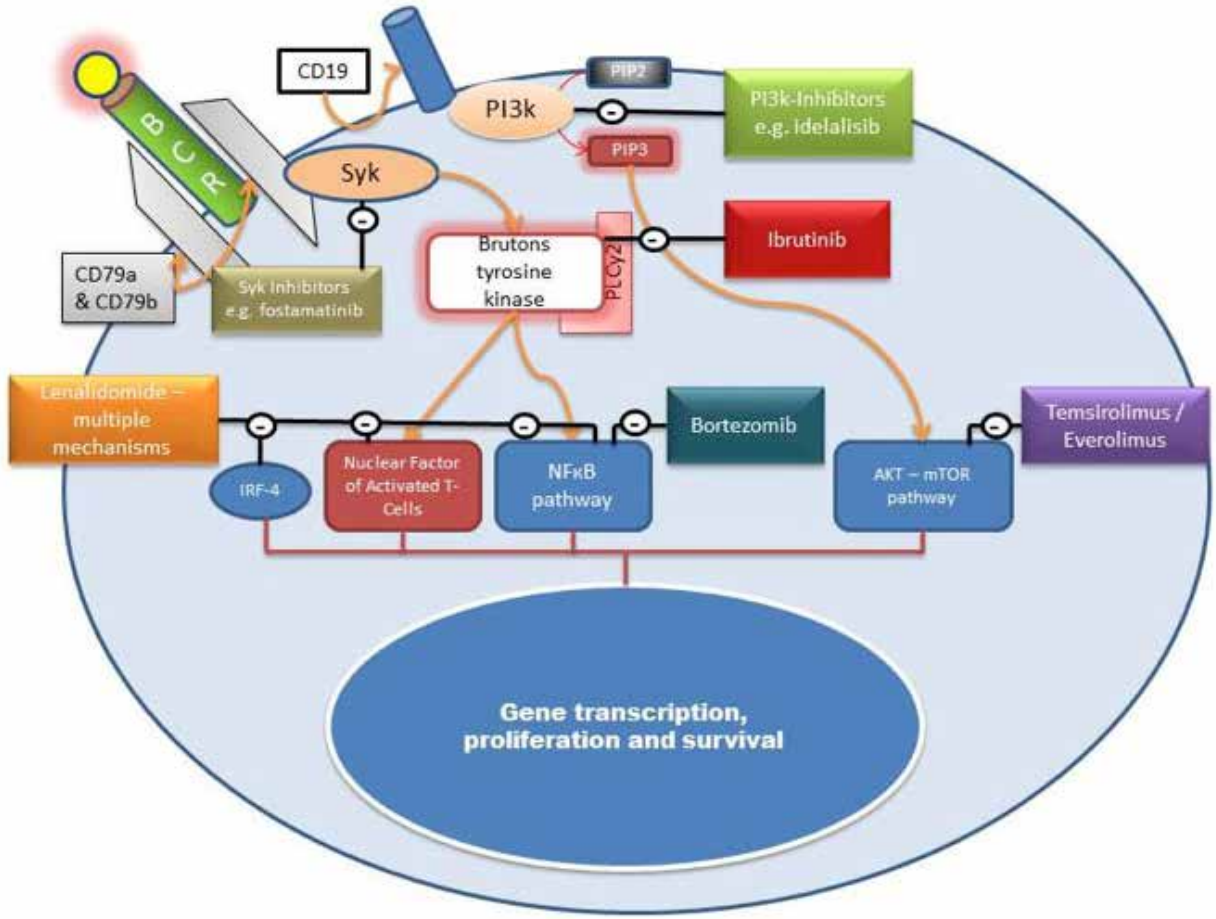
42. Cook G, Smith GM, Kirkland K, et al. Outcome following reduced-intensity allogeneic stem cell transplantation (RIC AlloSCT) for relapsed and refractory mantle cell lymphoma (MCL): A study of the British society for blood and marrow transplantation. Biol Blood Marrow Transplant. 2010;16(10):1419-1427. doi:10.1016/j.bbmt.2010.04.006.

43. Magnusson EA, Cao Q, Linden MA. Autologous and Allogeneic Donor Transplantation for Mantle Cell Lymphoma in Rituximab Era: Impact of Pre-Transplant Burden On Survival. In: ASH Annual Meeting.; 2012:120:3092.

44. Wang ML, Blum K a, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib : updated safety and ef fi cacy results. 2015;126(6):739-746. doi:10.1182/blood-2015-03-635326.Presented.

45. Furtado M V, Clarke K, Medd P, Hunter H, Rule SAJ. The use of Bruton's tyrosine kinase inhibition as a bridging strategy to successful allogeneic stem cell transplant in relapsed mantle cell lymphoma. Leuk Lymphoma. 2015;19(June):1-2.

Figure 1. An overview of targeted therapies currently in clinical use in mantle cell lymphoma and their relative position within the B-cell intracellular signalling pathway



Normal stimulation of the B-cell receptor (BCR) initiates a cascade of down-stream events. Phosphorylation of CD19, the B-cell co-receptor also occurs at this point, leading to generation of phosphatidylinositol-3, 4, 5-triphosphate (PIP3) from its bisphosphate precursor (PIP2).

PIP3 phosphorylates Brutons tyrosine kinase (Btk) directly while Syk phosphorylates the B-cell linker protein (BLNK) and phospholipase-$_{\gamma}$2 (PLC $_{\gamma}$2) which associate with Btk.

This ultimately triggers activation of nuclear-factor κ-B (NF-κB) which, together other key transcription factors including IRF-4 and nuclear factor of activated T-cells (NFAT), regulate proliferation and cell-survival through gene-transcription.

These pathways are constitutively upregulated in MCL cells and the target of several therapeutic agents. Lenalidomide has multiple direct and indirect mechanisms involving B, T, natural killer (NK) and dendritic cells.

BSBMT EDUCATION DAY

14TH OCTOBER 2015

I usually begin these little reports by telling you that, as usual, the BSBMT education day was held at SOAS - as this has become our regular haunt. However, dear reader, on this occasion I must announce that, owing to a student protest at SOAS, we were subject to an 11th hour relocation to BMA house in Tavistock Square. We must be grateful to the protesting students of SOAS. This was the first time I had had cause to visit the headquarters of the BMA and I, along with many of the other delegates, was delighted to see that my subscriptions to this institution over the years had not been in vain, as we were ushered into the palatial Great Hall to take our seats.

Allo-SCT for MDS

Professor Tony Pagliuca (King's College Hospital) spoke on the subject of HSCT for MDS. Prof Pagliuca pointed out that when he first approached Professor Goldman to discuss his plans to start performing allo-SCT for MDS he was met with a decidedly raised eyebrow. However since that time MDS transplantation has expanded to the point where it has overtaken ALL and is now the second most frequent indication for allo-SCT in Europe. MDS is a continuum of disease, having overlaps with AA, MPN and, of course, AML. King's have analysed the outcomes of their MDS allo-SCT by risk category and demonstrated equivalent outcomes for good, intermediate and poor risk disease with 5 year OS of between 40-50% for all categories. The MDS patient group with an unmet need remains those with a monosomal karyotype, for whom outcomes remain very poor despite HSCT.

There are numerous mutations described in transcription factors, tyrosine kinases, splicing factors, epigenetic regulators and other genes in MDS. Of these the most significant is P53; mutations in this gene are associated with very poor outcomes as demonstrated by both the King's data and the Bejar group at UCSD. Prof Pagliuca stated that, given the significant impact of the mutational analysis in MDS prognosis, future publications in the field will require these data to be present in order for them to be meaningful.

The main problem following allo-SCT for MDS is relapse and there are a number of strategies that might be undertaken in order to reduce this risk. These can be categorised as pre-HSCT, HSCT conditioning-based and post-HSCT strategies. Before proceeding to transplant for MDS with excess blasts, most haematologists would want to optimise disease response to a CR where possible. There is disagreement as to how best to do this, with some authors advocating azacitadine as equivalent to induction chemotherapy as a disease-reduction strategy. Data were presented that Prof Pagliuca felt supported the use of induction chemotherapy over azacitidine wherever possible: The CR rate in the AZA-001 study with azacitidine was inferior to that obtained with standard chemotherapy; there are data to suggest that Aza is ineffective in eradicating leukaemic stem cells and Professor Kroger has presented data that demonstrate significantly improved outcomes for allo-SCT performed with MDS that is in CR before transplantation.

When it comes to conditioning intensity there are data to suggest that, other than minimally intensive regimens, intensity is not a significant factor in determining outcome. Post transplant strategies to diminish relapse rate include withdrawal of immunosuppression, DLI based on chimerism, hypomethylating agents, cellular therapies and combinations of these options. Considering DLI, the King's data demonstrate a 80% 5 year OS and 65% EFS for a pre-emptive

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DLI strategy following allo-SCT for MDS, although this comes at a cost with a 31% GvHD incidence and a 19% incidence of chronic extensive GvHD. Victoria Potter's phase II study of structured vs. chimerism-directed DLI is expected soon and Prof Pagliuca urged support for this trial.

Other post-transplant strategies that may show promise include the use of post transplant azacitidine, which may upregulate GvL-target tumour antigens in MDS. Looking further afield more directed cellular therapies (such as CAR T-cells) may have something to offer in the on-going attempt to deliver greater anti-tumour activity with less off-target cell mediated toxicity. The development of MRD strategies in MDS may contribute to the guided use of these post-transplant interventions.

Management of Philadelphia-positive ALL

We then welcomed **Professor Oliver Ottmann** who has recently moved from Frankfurt to join the department at Cardiff University. He addressed a number of questions in Philadelphia positive ALL. There have now been 11 prospective clinical trials in this disease where induction has been achieved through the use of imatinib and chemotherapy, all of which have reported CR rates of 90-100%. Recent data from the GRALL group have demonstrated that intensive chemotherapy may not be necessary, as 800mg of imatinib combined with vincristine and dexamethasone produced a lower rate of induction death than the same imatinib dose with HyperCVAD and, because of this, an improved CR rate when compared to the more intensive regimen. There were no significant differences in survival between the two regimens at 3 years.

The great hall BMA house

Results like these have raised the question of whether allo-SCT is still necessary in this disease. However, data from the Northern Italy Leukaemia Group and the maturing MD Anderson data indicate that, in adults, relapse following TKI-based induction remains a significant problem and that allo-SCT is the most effective strategy for reducing this relapse rate. The high relapse rate remains a problem—even for those achieving a deep molecular response to induction in terms of BCR-ABL transcript reduction. The reason for this may well be the very high frequency of T315I mutated BCR-ABL found in adult Ph+ ALL, conferring resistance to standard TKIs. T315I does not confer resistance to ponatinib and early data on induction with a ponatinib-containing regimen are looking promising, although toxicity appears to be an issue and the data are very far from mature.

The predictive value of MRD is probably better established in ALL than in any other disease, but questions remain as to what time point to use, what methodology to use to measure it, what level of MRD is significant and what intervention to use when MRD is detected. A recent comparison of international MRD labs has shown significant variation in results between them, especially at the lower levels of MRD detection. There are data to suggest that post-induction MRD is of less predictive value than that obtained during consolidation. Myeloablative allo-SCT can probably overcome the negative impact of positive MRD on outcome, whilst some adults with negative MRD can be safely left without transplant—although there is not yet a consensus on how to precisely identify this group.

Autologous SCT has rather fallen out of favour for ALL following the UKALL12 data on this modality. However, recent data from the CALGB group may re-awaken interest in ASCT with good outcomes reported. Alternative donor transplantation is also an expanding area in Ph+ ALL with data from 2 Chinese groups suggesting that this may be a feasible option.

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The morning's Q&A panel: Prof Jane Apperley, Prof Tony Pagliuca, Prof Oliver Ottman and Prof J Snowden

In terms of post transplant manipulations, unlike in MDS, there is an obvious therapeutic choice in Ph+ ALL with a clear role being defined for the use of post-transplant TKIs in this disease. Studies examining whether to use a planned pre-emptive TKI strategy post transplant or an MRD directed approach—restarting TKIs if and when BCR-ABL transcripts become detectable, have demonstrated no difference in outcomes for these two approaches.

Future directions for this disease may include the further reduction of induction chemotherapy intensity, the elimination of the need for HSCT in some patients, the development of other strategies to overcome BCR-ABL resistance and the introduction of new pharmacological and cellular therapies.

Transplant for myeloproliferative neoplasms

Professor Jane Apperley (Imperial College London) spoke on transplantation for MPNs and began with myelofibrosis.

The first papers describing allo-SCT for this disease reported high TRM with myeloablative conditioning and, whilst RIC has reduced that, it has come at the expected cost of a higher relapse incidence. The number of allo-SCT being performed for MF being reported to the registries have been steadily increasing and it is on this background that Professor Kroger's consensus statement was published in Leukemia in 2015. Data from a large German/Italian series clearly demonstrate the importance of the DIPPS score in selecting patients for transplant—those with low risk disease have a significantly greater chance of survival with a non-transplant strategy; for intermediate-2 and high risk MF the situation is reversed, with significant survival benefit associated with allo-SCT. Data such as these have influenced the consensus statement which concludes that allo-SCT should be considered for all int-2 and high risk MF and for int-1 disease in patients <65 years old with >2% circulating blasts. Other MF patients should not be considered as HSCT candidates.

So much for patient selection, what about conditioning regimen and donor? The consensus document concludes that the intensity of conditioning should be based on age, co-morbidity and disease stage. A spectrum of RIC regimens have demonstrated acceptable TRM and OS outcomes and there is no direct evidence to favour one regimen over another. When it comes to donor selection, matched related donors are superior to matched-unrelated donors, who are superior to mismatched unrelated donors, but the differences between these groups are slight.

Splenomegaly is clearly a prominent feature of MF and may be implicated in the higher rates of engraftment failure seen in allo-SCT for this disease. At present there is not enough evidence to support splenectomy and splenic irradiation pre-transplant is not recommended. A third option (at least in places where drug funding permits) might be pre-transplant ruxolitinib. Numbers for this strategy are still small, outcomes appear to be better for patients responding to ruxolitinib therapy at the time of transplant. If ruxolitinib is to be stopped pre-transplant it should be carefully weaned to avoid the development of rebound symptoms.

Turning to CML Professor Apperley noted that in the year 2000 CML was the most frequent indication for allo-SCT in Europe. The current number of allo-SCT being performed for CML is 10-15% of that being performed in 1999 and, unsurprisingly, late phase CML allo-SCTs now outnumber those being done for early phase disease. One question is whether these transplants should be performed earlier. What is clear is that the outcomes of allo-SCT performed in blast crisis are dismal.

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Of patients presenting in chronic phase CML treated with imatinib first line, 60% will achieve a durable response and of those 40% may reach a trial of treatment withdrawal - these patients amount to perhaps 15% of all CML. Of the 40% who start imatinib in chronic phase and then move onto a second generation TKI, 50% will subsequently move onto a third generation TKI. Of this 50% half again will fail TKI treatment and require alternative therapy. In terms of third line treatment ponatinib may be more effective than alternatives. In patients responding to second generation TKIs but with issues of intolerance it may be worth changing to an alternative second-generation agent before moving to third line treatment.

Vaccination post-HSCT

The afternoon began with **Dr Paul Miller** (Anthony Nolan) who is working on the role of vaccination post HSCT. He has begun his researches by conducting a survey of vaccination practice at BSBMT centres and reassuringly he tells us that of the centres that have responded so far 100% recommend post HSCT vaccination and 92% of respondents have an SOP for this.

Antibody levels to vaccine preventable diseases (VPD) decline after HSCT and continue to decline for at least 7 years post-transplant, with a bigger decline after allo-SCT than auto. There are very limited published data on the incidence of VPD after HSCT. There is certainly an increased risk of flu and invasive pneumococcal disease. There are of course vaccines directed against both these organisms, but it is questionable as to whether the correlate of protection derived for these vaccines in a normal population can be generalised to the post HSCT population.

In the case of influenza, current IDSA guidelines recommend the tri-valent flu vaccine from 6 months post HHSCT or 4 months in the case of an active outbreak. The seroconversion rates following flu vaccination are very low in the first 6 months post HSCT and low up to 12 months. Beyond 2 years the seroconversion rates are as for immunocompetent individuals.

For Pneumococcus two vaccine formulations are available: the 23 valent, low-affinity, T-cell independent polysaccharide vaccine (PSV) and the 7 or 13 valent, T-cell dependent higher affinity conjugate vaccines (PCV). The 2013 IDSA guidelines recommend 3 doses of the PCV to 12 months post-transplant and PSV beyond 12 months in the absence of GvHD. PCV is more immunogenic than PSV and PSV gives a particularly poor seroconversion rate in the presence of cGvHD, where a 4th dose of PCV is recommended instead.

Future directions in this field may include the use of alternative vaccine delivery routes, the development of universal influenza vaccines directed against non-variant proteins and the development of new measures of correlates of protection for vaccination, including the possibility of developing assays to measure cellular correlates of protection.

Dr Fiona Dignan (Manchester) then presented her work on the joint BCSH/BSBMT guideline on the management of veno-occlusive disease (or sinusoidal obstruction syndrome as it's now calling itself). I won't summarise her talk here as that is done much better by directing you to her excellent guideline on the BCSH website.

Mr Derek Rosario (Sheffield) is a consultant urologist and has worked with Prof John Snowden in the thorny area of managing post-transplant haemorrhagic cystitis for many years. He began by informing us that there was no evidence to guide practice in this area, fortunately as this was an audience of stem cell transplant doctors, this news did not fill anyone with an overwhelming sense of panic.

The incidence of haemorrhagic cystitis (HC) post allo-SCT is estimated to be between 12 and 50% and it carries significant morbidity. It is graded in severity from grade I (dipstick positive haematuria) to IV (clot retention and renal impairment). There are numerous potential causes including the drugs and radiotherapy used to condition HSCT, coupled with thrombocytopenia and coagulopathy. Post-transplant BK virus, CMV and adenovirus can all be potential causes (exacerbated by thrombocytopenia and coagulopathy) but BK is the biggest culprit. BK is a polyoma DNA virus named after the initials of the patient it was first described in. It was first reported in haemorrhagic cystitis following HSCT in 1985. 90% of adults are seropositive for the virus, which is likely acquired during a respiratory infection and which then lies dormant in the renal interstitium and urothelium. Rigid cystoscopy with bladder washout can contribute to both diagnosis and management, but bladder ultrasound is probably the starting point in terms of visualising the problem. There is no role for biopsy and the diagnosis is confirmed by the detection of BK virus by PCR in blood and urine, where the peak copy number precedes the development of HC by about 14 days. BK virus copy numbers in urine of $>10^{10}$ copies/ml are sensitive but not specific for the diagnosis.

Management of HC requires a multi-disciplinary approach with analgesia, platelet transfusion, hydration, review of the level of immunosuppression

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and psychological support all being important supportive measures. Many cases are self-limiting but if the condition worsens it's time to call your friendly urologist for help; systemic treatment with quinolones, cidofovir and leflunomide have all been tried and may be of benefit. Intravesical treatment can involve bladder irrigation and clot evacuation via a three-way catheter. Alum irrigation, prostaglandin E1 treatment and hyperbaric oxygen may also have roles. There are reports of the use of intravesical cidofovir, for which the supporting evidence was described as level 4J! If none of this helps then dramatic measures may be needed, including bladder-bypass with nephrostomies, internal iliac artery embolization and, *in extremis*, cystectomy and urocutaneous diversion. I think that anybody who has cared for a patient with an intractable case of this post-transplant complication can vouch that the morbidity can be severe and the management challenging.

TMA and HSCT

Dr Sonata Jodele (Cincinnati Children's Hospital) spoke on the subject of thrombotic microangiopathy (TMA) following HSCT. This is a multiorgan disease the pathogenesis of which is associated with endothelial injury and complement activation. According to the published criteria Dr Jodele's 2014 study reported that the incidence of TMA following paediatric HSCT is 30-40%. This seems a high number, but the criteria are essentially laboratory-based rather than necessarily founded on clinical features. In this study proteinuria and markers of terminal complement activation (elevated sC5b-9) were poor prognostic factors. In a trial of giving eculizumab these patients the outcomes were better than those reported for historical controls. This treatment makes transplantation a financially toxic treatment, with an estimated cost per patient for eculizumab of $215,000.

There are genetic factors in predisposition for TMA; genetic variations in the ADAMSTS 13 and complement genes can lead to a very significant increase in the incidence of TMA following HSCT.

Late effects

The ultimate aim of a stem cell transplant is to get your patients to a position where they can experience late effects, but how do we prevent and manage those late effects when they do occur? **Professor Andre Tichelli** (University Hospital Basel) took us through the metabolic syndrome associated with late effects. By 2020 there will be 1 million long-term survivors of HSCT. Sixteen percent of survivors more than 5 years from HSCT die of cardiovascular disease, this incidence continues to increase with time from transplant and the rate of cardiovascular disease is both higher and occurs earlier in HSCT recipients than in the general population. The rates are also significantly higher for allo-SCT than ASCT. Hypertension, dyslipidaemia and diabetes are all more frequent in the HSCT population.

Some of these effects are due to radiotherapy and this is supported by the data from studies in Hodgkin's disease. TBI is associated with increased rates of diabetes and dyslipidaemia, likely due to its effects on the pancreas. Radiotherapy also contributes to direct endothelial injury and cranial radiotherapy increases the rate of insulin resistance. Hypogonadism, growth hormone deficiency and hypothyroidism all contribute to the cardiovascular risk following HSCT. Whilst the BMI of HSCT patients is often normal, this may disguise a relative loss of muscle mass with increased abdominal obesity. Myocyte insulin receptors are more efficient than adipocyte receptors, meaning that this pattern leads to increased insulin resistance and decreased glucose clearance. In children post-HSCT, 50% have insulin resistance and this figure is higher for those who received TBI in their conditioning. Of long-term adult HSCT survivors 35% have the metabolic syndrome compared to 15% of the general population. In addition to all these factors GvHD adds to the risk by causing endothelial injury and multiplying the effects of the other risk factors (hypertension, diabetes and dyslipidaemia).

Can these risks be mitigated? Professor Tichelli recommends screening early (from 1 year) and not waiting until immunosuppression has been stopped. Remembering that HSCT itself is a risk factor for cardiovascular disease means that these patients are high risk by definition and should be managed with lifestyle advice and treatment for dyslipidaemia with statins, which are the drugs of choice even in cases of hypertriglyceridaemia. As any diabetologist will tell you, compliance is a major problem in managing this long-term risk.

And thus the day concluded and, a little older, a little wiser we trudged from the palaces of the mighty to return to our hospitals to prepare ourselves for another year of transplantation; safe in the knowledge that we had, once again, been educated by the BSBMT.

Patrick Medd

CUTANEOUS GRAFT-VERSUS-HOST DISEASE FROM A DERMATOLOGIST'S PERSPECTIVE

Rubeta N Matin, Consultant Dermatologist, Oxford University Hospitals NHS Foundation Trust

Following allogeneic stem cell transplantation, GVHD is a major cause of morbidity and mortality with the commonest organs affected being the skin and oral mucosa. The British Committee for Standards in Haematology GVHD guidelines recommend organ-specific management and supportive care[1], recognising that early input from a Dermatologist is likely to improve clinical outcomes[2]. However, to date, there are no reported models for the optimal delivery of a dermatology service for GVHD patients.

Clinical presentation of cutaneous GVHD is widely variable and a degree of GVHD is desirable for a graft-versus-malignancy effect. A dedicated GVHD clinic reported that 13/30 referrals were made to Dermatologists with a specialist interest in GVHD[3]. At Oxford University Hospitals NHS Foundation Trust, we sought to address this potential unmet need by providing a dedicated dermatology service in parallel with the Bone Marrow Transplant (BMT) clinic in the Haematology outpatient department. We demonstrated that Dermatology input was required in up to 40% patients in the BMT clinic over a nine-month period and patient reported outcomes and experience were very good. A dedicated Dermatology service enables accurate and early diagnosis of cutaneous and oral GVHD. This can improve morbidity through appropriate and timely use of local and topical treatments and potentially avoids the need for prolonged systemic immunosuppression. Additionally, specialist Dermatology input allows diagnosis and management of a diverse range of skin diseases (other than GVHD) that affect patients post-transplantation.

Traditionally GVHD was defined as acute and chronic based on time post-transplantation, but more recently the two are distinguished by clinical and pathophysiological features.

The inflammatory changes that predominate in the initial phases are mainly due to a reaction to the graft. Autoimmune reactions and immunodeficiency develop in later phases, and over time the reparative process can lead to fibrosis in tissues. Acute GVHD is described by a 3-phase model consisting of 1) a conditioning regimen causing damage to keratinocytes in a pro-inflammatory environment, 2) presentation of antigens to donor T cells by the host dendritic cells, followed by activation of donor-derived T cells, and 3) activation of a type-1 helper T cell response that leads to necrosis of keratinocytes[4].

In contrast, chronic GVHD involves both allogeneic and autoimmune reactions. Once the thymus is damaged in the conditioning regime and/or by acute GVHD, host tolerance of its own cells is impaired. A complex response develops and CD4+ and CD8+ T cells, regulatory T cells, and B cells all produce autoantibodies. Th1, Th2 and Th17 responses produce pro-inflammatory cytokines that then cause fibrosis and can subsequently lead to organ failure[5].

This article focuses on the diverse clinical presentation and management of cutaneous GVHD and addresses some practical issues clinicians face in the BMT follow-up clinic. It aims to help clinicians more effectively treat post-allogeneic stem cell transplant patients with cutaneous GVHD, focusing mainly on skin-directed therapies.

Acute cutaneous graft-versus-host disease

Acute GVHD is considered 'classic' if the onset occurs within 100 days of allogeneic stem cell transplantation, 'persistent' if it lasts beyond 100 days, 'recurrent' if it resolves but reappears after 100 days, and 'late-onset' if symptoms start after 100 days.

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It can also occur in allograft recipients following a rapid wean in dose of immunosuppressant agents or following donor lymphocyte infusions. The clinical signs and symptoms and underlying pathophysiological mechanisms are distinct to those seen in chronic cutaneous GVHD.

Acute cutaneous GVHD usually presents with sudden onset of a burning or pruritic morbilliform rash. This may be preceded by subtle peri-follicular prominence (erythema / scaling around the hair follicles on limbs).

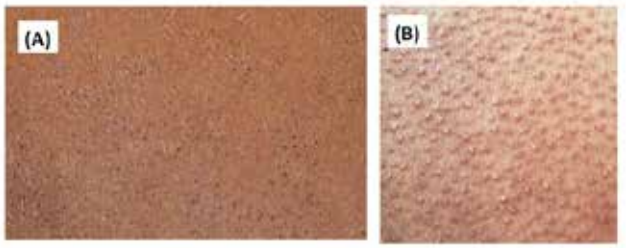


Fig 1: Keratosis pilaris

(A) Perifollicular scale

(B) Follicular prominence and peri-follicular erythema

At first there is macular blotchy erythema +/- dysaesthesia or oedema affecting palms, soles and face, and commonly also involving pinnae, cheeks, lateral neck, and upper back. The scalp is usually spared. If severe, the patient can become erythrodermic (erythema affecting more than 90% body surface area). Mucosal involvement is common, especially the conjunctivae and the oral cavity. Generalized erythema, blistering, and erosions simulate toxic epidermal necrolysis in severe acute GVHD and under these circumstances management of the skin should always be instigated in conjunction with Dermatology.

In most cases of acute cutaneous GVHD, there are other features that confirm the diagnosis including fever (culture-negative), gastrointestinal symptoms e.g. abdominal pain, nausea, vomiting, and watery/bloody diarrhoea and abnormal liver function. Skin biopsies from a well-established peri-follicular lesion can sometimes help to distinguish between acute GVHD and other diagnoses e.g. drug eruptions, although this can prove challenging even for experienced dermatopathologists. Potent topical corticosteroids may control mild acute cutaneous GVHD, but severe cases require high-dose systemic corticosteroids.

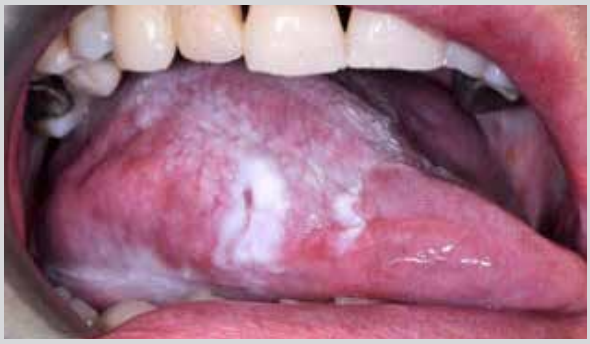
Other treatment options include immunosuppressant agents, anti-TNF antibodies and extracorporeal photopheresis (ECP). The main approach to acute GVHD management is prevention in the first place.

Chronic cutaneous graft-versus-host disease

Chronic GVHD can appear as an extension of acute GVHD (the progressive chronic form), or it can follow a disease free period (the quiescent form) or develop without prior GVHD signs (the de novo form). In chronic GVHD, the skin is affected in 75-100% of cases and the oral mucosa in 80-100% cases. It is important to remember that other mucosal surfaces can also be involved and should always be considered when examining patients.

Box 1: Mucosal involvement in GVHD

Oral cavity - with lichen planus-like lacy white buccal involvement (early diagnostic sign)



ulceration, mucoceles, hyperkeratosis, sclerosis and fibrosis (late – patients report difficulty moving tongue when chewing). When the salivary glands are involved patients may report pain, dryness, abnormal taste sensations, hypersensitivity, and dental caries. Viral or fungal infections especially oral candidiasis are common.

Eyes with burning, irritation, dryness, and photophobia.

Vulvovaginal dryness, pain, erythema, lichen planus-like changes (diagnostic), lichen sclerosus-like changes, and strictures – many patients will not report these symptoms unless directly asked.

Penile irritation, soreness, erythematous plaques on penile head, lichen-sclerosus like changes, difficulty retracting the foreskin

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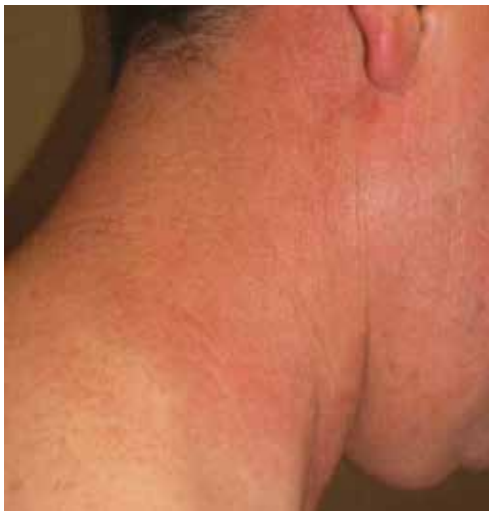

Figure 2:
Photosensitivity demonstrated by erythema of exposed skin with sharp cut-off where skin is covered by clothing.

Photosensitivity is the one of the commonest reported skin diseases post-transplant particularly for individuals who did not previously experience sensitivity when exposed to natural sunshine prior to their transplant. This manifests as erythema or skin disease that is accentuated in a UV-exposed distribution i.e. affecting face, neck, central 'V' of the chest. [Figure 2]

There are numerous skin manifestations of chronic cutaneous GVHD, with one form evolving into another or overlapping patterns co-existing within the same individual for example a combination of lichenoid and sclerodermoid features.

The major clinical categories of chronic cutaneous GVHD are detailed in Table 1 (below). Clinical features of chronic cutaneous GVHD include: lichen planus like changes [figure 6], poikiloderma [figure 7] and dyspigmentation [figure 8] - see page 22.

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Table 1: Clinical presentation of chronic cutaneous GVHD

Clinical findings	Description	Skin-directed therapies
Xerosis/ichthyosis	Dry skin Very common	Emollients ++
Keratosis pilaris-like [Figure 1 - page 20]	Follicular prominence, peri-follicular erythema, 'hedgehog' appearance of skin	Emollients containing urea or salicylic acid (e.g. Flexitol®, Eucerin lotion®, Calmurid lotion®)
Lichen planus-like* [Figure 6 - page 22]	Purple / hyperpigmented papules / plaques often on extensor surfaces, acral predisposition	Potent topical steroids, topical tacrolimus, phototherapy (psoralen plus UVA)
Poikiloderma* [Figure 7 - page 22]	Telangiectasia + dyspigmentation + epidermal atrophy	Often asymptomatic – no specific treatment required, consider potent topical steroids
Dyspigmentation [Figure 8 - page 22]	Post-inflammatory hyperpigmentation or vitiligo-like hypopigmentation	Use topical steroids if erythema co-exists suggesting active GVHD
Acral erythema	Erythema, oedema, pain (can appear out of proportion to clinical signs) +/- hyperkeratosis	Superpotent topical steroids +/- salicylic acid if hyperkeratosis. Consider oral steroids.
Morphoea/ Sclerodermatoid* [Figure 3 & 4 - page 22]	Superficial or deep sclerotic patches / plaques	If superficial consider PUVA or UVA1 phototherapy, if deeper +/- other organ involvement, consider increased immunosuppression or extracorporeal photopheresis. Consider referral to physiotherapist.

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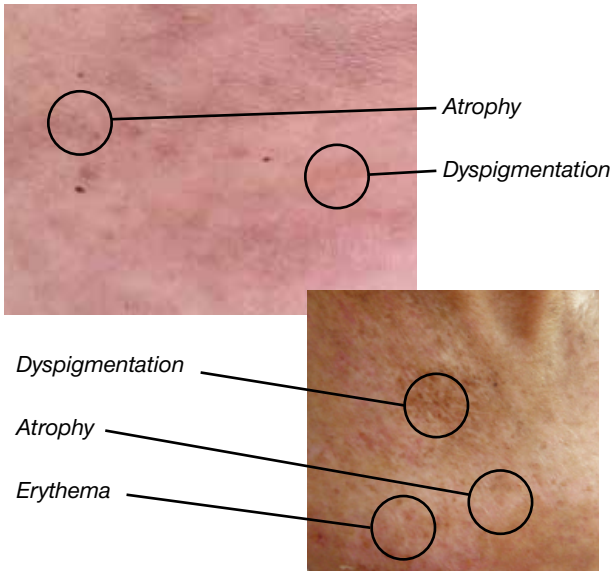
Figure 6:
Lichen-planus like/ lichenoid skin changes – scaly purplish plaques largely affecting extensor surfaces.

Figure 7:
Poikiloderma – combination of dyspigmentation, atrophy (thinned skin) and erythema.



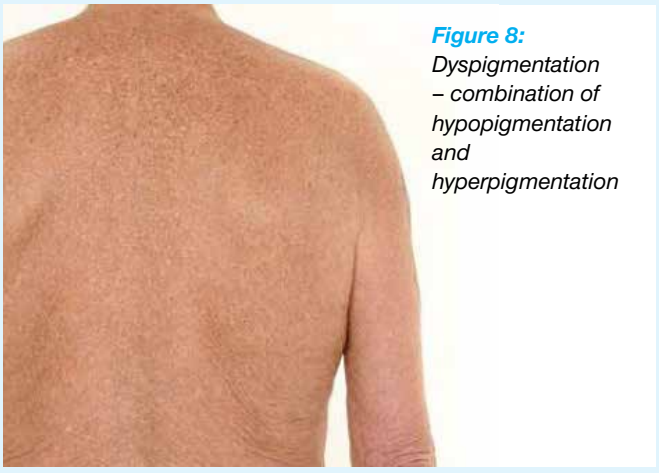


Figure 8:
Dyspigmentation – combination of hypopigmentation and hyperpigmentation

Sclerodermoid disease is the most serious form of cutaneous GVHD because if left untreated is irreversible. The superficial form is morphoea-like [Figure 3] and deep sclerotic disease is scleroderma-like [Figure 4]

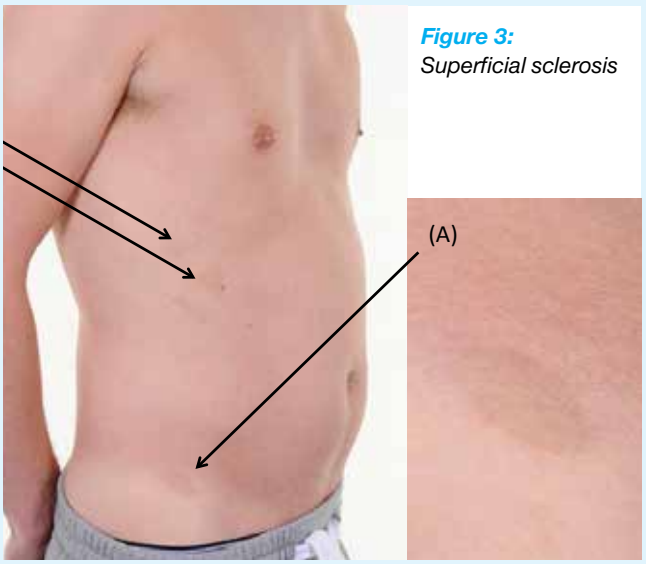


Figure 3:
Superficial sclerosis

Figure 4:
Deep dermal sclerosis

This form of GVHD demonstrates isomorphic response (localised to sites of minor skin injury or pressure e.g. waistband) and isotopic response (occurs at sites of previous skin damage e.g. varicella zoster infection and central line venepuncture sites). An early feature of sclerodermoid disease is whole body generalised oedema and/or loss of hair. Blistering and ulceration can occur in sites of active sclerodermoid disease and is thought to confer a poorer prognosis. Consider co-existing herpes viral infection if vesicles/erosions are present and if the skin is very painful. Swabs should always be sent to exclude primary or co-existing bacterial, viral or fungal infections. Potent topical steroids under hydrocolloid dressings can help with healing once infection has been excluded.

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Punched out ulcers are commonly seen in sclerodermoid skin and healing can take weeks to months [Figure 5]. Sclerotic disease over joints limits movement and can cause significant functional impairment.

Figure 5:
Deep punched-out ulcers develop at sites of friction. Swabs should be sent to exclude co-existing infections.

GVHD can affect any mucosal sites and enquiry should be made particularly if there is cutaneous involvement [Box 1 - see page 20]. Many patients may be too embarrassed to discuss genital involvement until it is severe, when scarring may be difficult to reverse. Signs of GVHD affecting the hair can include brittle hair, premature greying and scarring alopecia. Loss of body hair and sweat glands can cause heat sensitivity. Nail involvement occurs in up to 50% of patients with chronic GVHD and includes nail dystrophy, longitudinal ridging, thinning, fragility, scarring (pterygium) & loss of nails (signs similar to those seen in patients with lichen planus).

Management of cutaneous GVHD

Management of GVHD is challenging. The evidence-base supporting treatment choice for cutaneous GVHD is limited for many reasons: the wide phenotypic spectrum of skin disease, lack of validated outcome measures and poorly designed or conducted RCTs mean that studies are not sufficiently powered to measure responses according to disease subtype.

General advice should be given to all patients irrespective of a prior history of acute GVHD [Box 2]. Ichthyosis (very dry skin) is common and can be very symptomatic and itchy. Prescribe large quantities of emollient (500 grams) as effects are short-lived and encourage patients to apply these to all their skin regularly.

BOX 2: Skin management advice to all allograft transplant recipients.

1) General advice

Most patients report that their skin is much drier post-transplant so they should use:

a) Emollients – applied regularly and liberally at least 2 – 3 times daily

b) Use soap substitutes (e.g. Dermol lotion®) or bath additives (Oilatum® or Balneum® range) when bathing / showering to improve hydration of the skin

2) Photoprotection

Ultraviolet light exposure can trigger a flare of GVHD and can prolong or worsen cutaneous GVHD. UV light can also trigger phototoxic drug eruptions e.g. voriconazole, non-steroidal anti-inflammatory drugs. The risk of skin cancer is higher in patients with GVHD and this risk is already elevated by immunosuppressive agents and/or prior phototherapy treatment. Advice should include:

a) Avoiding the peak hours of sunshine (11am – 3pm)

b) Using a broad spectrum sun screen SPF 30+ regularly

c) Using broad-brimmed hats, long sleeves, trousers or UV-protective clothing (physical methods of sun protection are more effective than relying on sunscreens)

3) Advise patients about self-skin examination

a) Be aware of erythematous rashes – they may not be symptomatic

b) Advise patients about identifying early signs of sclerotic chronic GVHD e.g. darkening or tightening of skin – commonly occurs at the waistband or under breasts, thickening of skin, rippling/dimpling of the skin, restricted range of motion and joints e.g. wrists, shoulders or ankles.

c) Advise patients to contact you if they notice any new or rapidly growing lump on the skin or any skin lesion which is slow to heal as this may indicate a new skin cancer.

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A number of different emollients may need to be tried before the patient finds one that is tolerable. These are best applied after a shower or bath. Smear the emollient in the direction of hair growth and allow to soak into skin. Advise patients not to rub the emollient into the skin, to minimize irritation or blockage of hair follicles (folliculitis). Emollients should be applied to both affected and unaffected skin.

Topical steroids are needed for active cutaneous GVHD. More than one topical steroid may need to be prescribed according to the body site affected; for the face/neck/genitals prescribe mild/moderate potency topical steroids in 30 gram tubes (sufficient for single application for 2 weeks); for the body, prescribe 100 gram tubes of moderate/high potency topical steroids.

Table 2: Examples of topical steroids according to potency

Potency of topical steroid	Examples
Mild	Hydrocortisone 1% / 2.5% Hydrocortisone with antifungal (used for inflamed flexural rashes when candidiasis may complicate treatment with corticosteroid).
Moderate	Clobetasone butyrate 0.05% [Eumovate®] Moderate with antibacterials and antifungals (clobetasone butyrate 0.05%, oxytetracycline 3% [as calcium salt], nystatin 100 000 units) [Trimovate cream®]
Potent	Betamethasone valerate 0.1%, Mometasone furoate 0.1% [Elocon®] Potent with salicylic acid, e.g. betamethasone 0.05% with salicylic acid 3% [DiproSalic ointment].
Superpotent	Clobetasol propionate 0.05% [Dermovate®]

Seek advice from a Dermatologist if you need to prescribe superpotent topical steroids or calcineurin inhibitors. Explaining to patients how much to apply and where to apply the creams is very important – otherwise compliance is likely to be sub-optimal. Specify the base where possible i.e. cream, ointment, lotion etc. – topical steroid ointments are preferred to creams because there is a greater risk of contact sensitisation from preservatives in cream formulations. Some patients may find ointments too greasy especially on the face. Topical steroids do not need to be applied more frequently than twice daily although once daily is often sufficient. Advise applying it 20-30 minutes before or after any emollient is applied.

Phototherapy has been reported to be an effective treatment for chronic cutaneous GVHD. Psoralen plus ultraviolet A light (PUVA) and ultraviolet A-1 (UVA-1) are both effective options in sclerodermoid disease. Narrowband UVB may be useful in lichenoid GVHD. Phototherapy should be considered for patients in whom additional systemic immunosuppression poses a high risk of infection or interferes with a graft versus tumour response. Dose modification is important in patients taking photosensitizing medications, and caution must be employed in patients with antinuclear autoantibodies. The potential benefit of phototherapy must be weighed against the elevated risk of cutaneous malignancy in immunocompromised patients, particularly those with actinic damage or a history of ionising radiation. Extracorporeal photopheresis (ECP) has demonstrated benefit in both sclerodermoid and non-sclerodermoid GVHD. Limitations of ECP include the time-intensive nature of the treatment (two consecutive treatments fortnightly) and restricted availability across the UK. The main advantage of ECP is its efficacy in extra-cutaneous manifestations of GVHD and decisions should be made jointly with specialists who have experience in providing ECP.

Skin disease has significant impact on quality of life and—even in the context of severe extra-cutaneous GVHD—mucosal and cutaneous involvement can be devastating to patients. Close collaboration with Dermatologists can allow patients to discuss their concerns fully, express their needs and ensure that the appropriate treatment is implemented for their skin. Co-existing alternative common skin conditions e.g. seborrhoeic dermatitis frequently occur and confirmation from a Dermatologist that this is not GVHD can be very reassuring to patients.

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In conclusion, the wide phenotypic spectrum of cutaneous GVHD underscores the need for a collaborative approach to management with Dermatologists.

BOX 3: When to refer to a Dermatologist
a) Diagnosis is not clear e.g. drug eruption versus GVHD or suspect alternative skin condition
b) Early superficial/evolving sclerodermoid skin disease
c) Suspected new skin cancer
d) Skin disease unresponsive to potent topical steroids for > 3 weeks
e) Skin ulceration
f) Skin disease impacting significantly on patient quality of life
g) Using topical calcineurin inhibitors (tacrolimus or pimecrolimus)

Transplant teams and Dermatologists should work closely so that both specialist groups have a better understanding of the complexity of these cases and the variables that determine treatment choices. Only through joint working can many of the unanswered questions in cutaneous GVHD be solved in the future.

Acknowledgements

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References

1. *Dignan FL, Amrolia P, Clark A, Cornish J, Jackson G, Mahendra P, et al. Diagnosis and management of chronic graft-versus-host disease. Br J Haematol. 2012;158(1):46-61.*
2. *Dignan FL, Scarisbrick JJ, Cornish J, Clark A, Amrolia P, Jackson G, et al. Organ-specific management and supportive care in chronic graft-versus-host disease. Br J Haematol. 2012;158(1):62-78.*
3. *Dignan FL, Manwani R, Potter MN, Ethell ME, Leonard H, Brennan J, et al. A dedicated GvHD clinic may improve the quality of life for allogeneic stem cell transplant survivors. Clin Transplant. 2013;27(1):E1-2.*
4. *Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet. 2009;373(9674):1550-61.*
5. *Sakoda Y, Hashimoto D, Asakura S, Takeuchi K, Harada M, Tanimoto M, et al. Donor-derived thymic-dependent T cells cause chronic graft-versus-host disease. Blood. 2007;109(4):1756-64.*

THE PRESIDENT'S COLUMN

I am delighted to be taking over the helm of the BSBMT as the new President from January 2017 at such an exciting time. I am sure you will all join me in thanking Charles Crawley for his excellent leadership over the past 2 years. As a member of the BSBMT Executive since 2008 I am well aware of the challenges ahead and of the achievements of the past and hope that we can continue moving the Society forward over the next couple of years. I firmly believe that our main aims should be to support all the hard-working Transplant physicians in the UK and ROI and to ensure access to transplantation for all patients that might benefit.

The year has started on a positive note with the recent announcement that NHS-England has now agreed to routinely commission second allogeneic transplants for relapsed patients meeting certain criteria. Following the disappointment that this was not funded last summer, this change of direction has been a major breakthrough (see policy on the following web-site for details https://www.england.nhs.uk/commissioning/spec-services/npc-crg/blood-and-infection-group-f/f01/) and all credit goes to the BMT-CRG and other organisations including the Anthony Nolan who have worked hard to provide sufficient evidence for this to be approved. Patients must have achieved at least a 12 month remission to their first transplant, be back in CR and be deemed fit enough to meet the criteria but I am sure many UK patients will benefit from this intervention going forward.

We are also thrilled at the launch of the new IMPACT Partnership for Accelerated Transplant Related Clinical Trials this spring. This exciting development for clinical research in stem cell transplantation has the potential to transform the UK's ability to deliver prospective clinical trials and improve outcomes for transplant patients. The overarching aim of IMPACT is to accelerate and facilitate the delivery of a portfolio of randomised phase 2 and 3 trials by UK transplant centres.

It is anticipated that 9-12 trials will be delivered over the four-year time period. By reducing set-up and creating new capacity, the IMPACT trials network represents an innovative development within the UK transplant community with the potential to accelerate trial delivery and improve patient outcomes whilst providing high-quality biological samples with matching clinical data, to drive basic scientific research. Many thanks to Prof Charlie Craddock and the UK Strategic Forum for driving this initiative forward and to NHS BT, Anthony-Nolan and Leuka for funding it. Prof David Marks has been appointed as the Medical Director and Centres have been invited to bid for funding for research nursing and to send trial proposals through for consideration.

Closer to home we are also pleased to announce that following the retirement of Keiren Kirkland last summer we have now completed the recruitment of her successor and welcome Julia Perry to her new role as Head of the BSBMT Registry. We were very sad to see Keiren depart as she has been such a vital part of the BSBMT over the years and has worked very hard to ensure the ongoing success of the Registry. As a long serving member of Keiren's team, Julia is in a fantastic position to continue the good work and ensure the future success of the Registry which provides invaluable data for the Commissioners and the Clinical Trials Committee.

In addition we say a fond farewell to Prof Gordon Cook who leaves the Executive after many years of Service, David Edwards (auto-only representative) and Karl Peggs who have completed their time on the Executive. In their place we welcome Dr Dominic Culligan (auto-only Representative) and Dr Eduardo Olivarria to the Executive and also congratulate Dr Kim Orchard who has been elected as the new President Elect.

Jenny Byrne