



# Graft Versus Tumour Effect

# 12

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## Abstract

The treatment of relapsed disease remains challenging, and it is well accepted that concept of allogeneic HSCT relies upon both the conditioning or preparative regimen used for the recipient and the graft versus malignancy (GvM) or leukaemia (GvL) effect provided by the donor T cells and NK cells. Strategies which involve harnessing this effect are crucial to success and need to be exploited and refined to improve outcome. Further research is required to identify new strategies and therapies to improve the outlook for patients who relapse post-HSCT.

The nursing challenges following relapse are immense; the psychological support required is complex and largely falls to the nurse to coordinate and deliver regardless of the selected treatment approach.

## Keywords

Graft versus malignancy (GvM) or leukaemia (GvL) • Donor lymphocyte infusions (DLI) • Relapse • Chimerism

## 12.1 Introduction

It is well accepted that concept of allogeneic haematopoietic stem cell transplant (HSCT) relies upon both the conditioning or preparative regimen used for the recipient and the graft versus malignancy (GvM) or leukaemia (GvL) effect provided by the donor T cells and NK cells. The autoim-

mune attack on the malignancy helps to eradicate the disease in the recipient with the aid of the conditioning regimen. The susceptibility of a malignant condition being eradicated by GvM or GvL effect varies with the most sensitive conditions being chronic myeloid leukaemia, chronic lymphocytic leukaemia, low-grade B-lymphoproliferative disorders, mantle cell lymphoma and EBV lymphoproliferative conditions. Most other conditions have an intermediate sensitivity to the GvM or GvL effect with conditions that have a special proliferation or that are advanced or chemo-refractory having the least response.

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## 12.2 Mechanism of GvM/GvL Effect

Both T lymphocytes and NK cells participate in the GvL effect, and it is believed that cytotoxic T cells recognise several classes of antigens on leukaemic cells. The NK cells target MAg self-proteins (present on the tissues of the recipient) which are overexpressed by the leukaemia, e.g. proteinase 3 and elastase tumour-specific antigens, e.g. Wilms tumour 1, and fused proteins, e.g. BCR-ABL, by using the perforin-granzyme pathway to kill their targets. However they are only activated when inhibitory signals from self (recipient) MHC class 1 molecules on the target are missing or overcome by activating signals through the NKG2D receptor. The suppressor of the recipient's immune system allows the donor cells to provoke this effect.

## 12.3 Minimal Residual Disease (MRD)

The purpose of monitoring MRD in the post-transplant setting is to track disease response or remission or low-level disease recurrence when the quantity of a particular marker starts to increase. This enables a therapeutic intervention to be implemented very early and may optimise the chance of success.

MRD can be monitored using molecular methods – this is where the underlying condition has a specific marker or protein that can be monitored by using flow cytometry. Table 12.1 shows the cytogenetic abnormalities that can be targeted in some diseases (page 410 Treleaven and Barrett 2009), and Table 12.2 shows some of the molecular targets (Apperly et al. 2012) if they were present at diagnosis.

## 12.4 Chimerism

Chimerism analysis is another important tool in the post-HSCT follow-up of the recipient. It demonstrates the degree of engraftment of donor

**Table 12.1** Common targets for MRD screening in different malignancies

Disease	MRD target
Myelodysplastic syndromes	Del(5q); monosomy 7, trisomy 8
Chronic myeloid leukaemia	t(9;22)
Acute myeloid leukaemia	t(8;21); inv (16)
Acute lymphoblastic leukaemia	t(9;22) t(4;11); t(8;14)
Follicular lymphoma	t(14;18)
Mantle cell lymphoma	t(11;14)
Chronic lymphocytic leukaemia	del(13q), del(11q); del(17p)
Multiple myeloma	del(13q), del(11q)

**Table 12.2** Examples of Molecular targets in different malignancies

Disease	Molecular target
B-ALL	TEL-AML1 BCR-ABL1 Ig/TCR gene rearrangements
T-ALL	Ig/TCR gene rearrangements Tald1
APML	PML-RARA
AML	AML1-ETO CBFb-MYH11 WT-1 NPM1 mutated FIT3

cells and offers the possibility to identify impending graft rejection and can also be an indicator of disease relapse or recurrence. Chimerism can also be used as a basis for treatment intervention to prevent graft rejection and maintain engraftment and is used as a mechanism to administer pre-emptive immunotherapy to provoke the GvM or GvL effect particularly in high-risk patients.

Chimerism allows the monitoring of the ratio of donor- and recipient-derived cells in non-genetically identical donor and recipient pairs. This allows for timely intervention in the care of the recipient. The term “chimerism” comes from Greek mythology where the chimera was a fire-spitting monster with the head of a lion, body of a goat and the tail of a serpent and is used to describe the fact of two entities – DNA from two people – existing in the one person.

Initially it was felt that in order for all HSCT to be considered successful, an individual would have to be 100% donor chimerism, and this is certainly the case with malignant conditions. However, in non-malignant conditions (e.g. aplastic anaemia or haemoglobinopathies), a mixed chimerism may be enough to restore normal haematopoiesis.

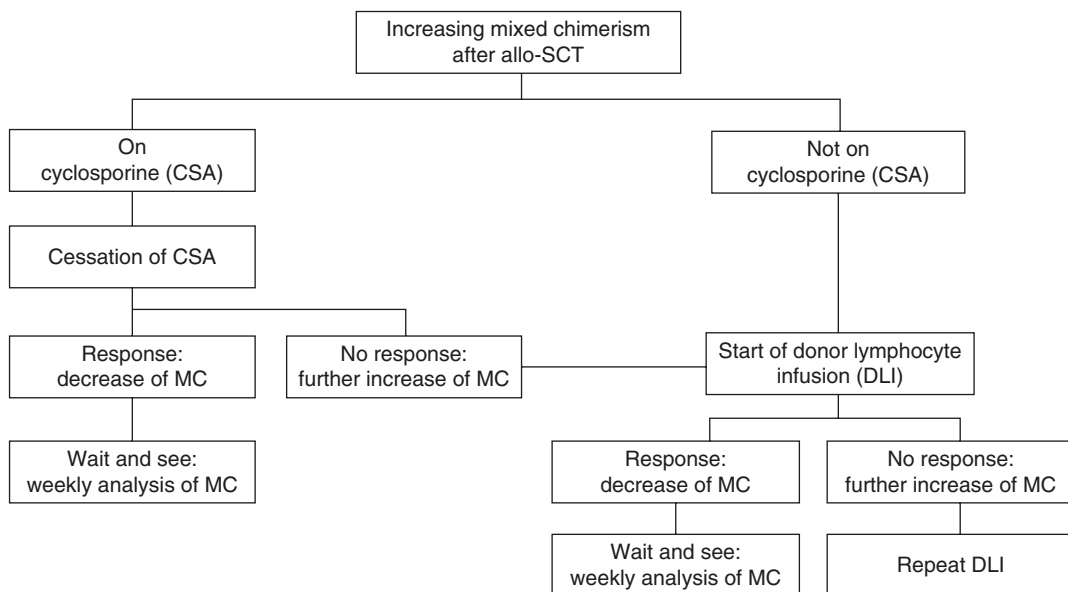
While the total (unfractionated) chimerism result is important, more information can be elicited if lineage-specific chimerism is performed allowing separate tracking of lymphoid and myeloid engraftment and in itself can provide very useful information about possible disease relapse. This should be used in conjunction with other means of MRD analysis and diagnosis.

Schedule and protocols for chimerism analysis are centre, disease and treatment specific, and reference should be made to your institution's policy.

## 12.5 Management of Relapsed Disease

When a recipient has evidence of MRD or a decrease in chimerism, there are a number of strategies that can be followed. In the case of mixed chimerism, the schema in Fig. 12.1 can be followed.

Relapse usually occurs in the BM but may also be at extramedullary sites, thought to be due to immune escape from patrolling lymphocytes. It is also thought that leukaemia can escape from the immune control provided by the donor's T cells by mutating or becoming a more resistant clone of the original disease. The cause of the relapse may also be different in different haematological malignancies. While relapses can occur many years after HSCT suggesting that perhaps the underlying disease was never eradicated and was held in control by the donor immune system, it is more common with CML, and in this disease, the administration of DLI can often restore remission.



**Fig. 12.1** Patients with increasing MC post transplant (5% or more autologous cells) compared to the previous sample are offered further therapy. Immunotherapy for patients receiving CSA consists of immediate discontinuation of the immunosuppressive agent. Chimerism is then assayed weekly until CC status is restored. If MC continues to increase after cessation of CSA, a DLI is given. Immunotherapy for patients not receiving CSA consisted of DLI as frontline treatment. The cell dose administered

is based on the number and potential severity of HLA mismatches between the donor and recipient, and starting doses range from  $2.5 \times 10^4$  to  $1 \times 10^6/\text{kg BW}$ . After DLI, chimerism status is assayed weekly until CC status is restored. Patients who show a further increase in MC are given an additional DLI after at least 3 weeks have elapsed. If no GVHD occurs, the dose of DLI is doubled (Bader et al. 2005)

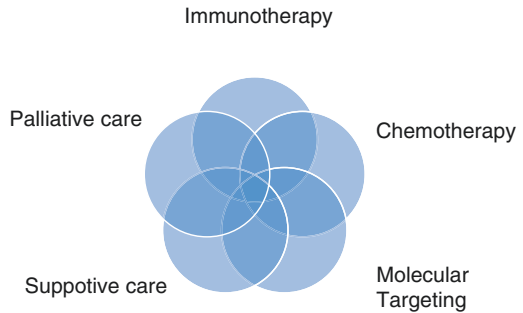
However the outlook for the recipient who relapses post-HSCT is poor and requires frank discussion with the recipient and their family to define the likely outcomes and success. Care for the relapsed patient revolves around five potential strategies:

- Immunotherapy
- Chemotherapy
- Molecular targeting
- Supportive care
- Palliative care

The timing of relapse is extremely important. Early relapses are difficult to treat, and any intervention may be challenging for the patient or precluded due to the proximity to the HSCT and complications experienced by the recipients. Patients who relapse after HSCT may find it extremely difficult to adapt to and accept the fact that further treatment may not be possible or may be ineffective particularly if they have already received intensive treatment prior to HSCT.

However, it is important to provide ongoing support so that patients do not feel abandoned at this stage, and this helps patients to maintain realistic levels of hope and optimism. Palliative and supportive care measures are valid and realistic options to help maintain a good quality of life and should not be ignored. The help and support of the medical team, recipient's local doctor, referring hospital and often primary care services, e.g. GP and hospice, are essential in the management and treatment of the relapsed patient. Referral to psychology, counselling or psychiatric teams may also benefit the patient and their family.

## 12.6 Treatment Options for Post-allogeneic HSCT Relapse



## 12.7 Management of Relapsed Disease

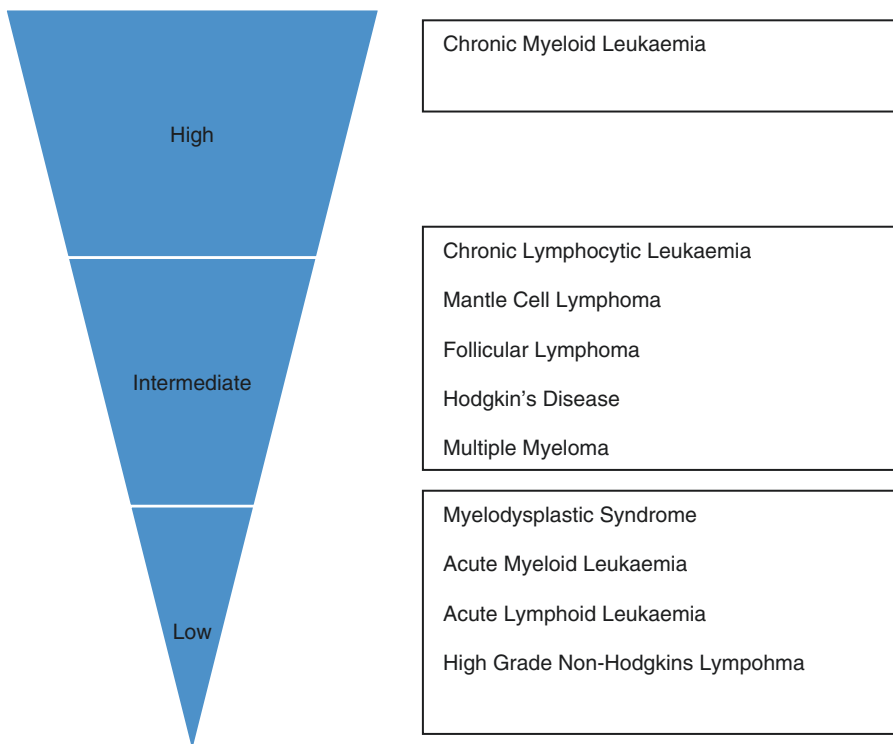
**Immunotherapy** This is an important tool in the management of the relapsed patient and can range from withdrawal of immunosuppression (if the patient is still on it) to the administration of donor lymphocyte infusions (DLI) infusions in incremental doses.

## 12.8 Withdrawal of Immunosuppression

The GvL or GvM effect of HSCT can be enhanced by reducing and stopping the IS (immunosuppressive) agent that the patient may be taking. Nursing care and education is essential in this circumstance as along with GvL the patient needs to be monitored for the development of GVHD which is extensively discussed in another chapter.

## 12.9 Responsiveness to DLI

(Adapted from Treleaven and Barrett 2009)



### 12.9.1 DLI

DLI alone can induce permanent remission of the underlying disease particularly in the case of CML where relapses occur at a molecular level. In other diseases, the response can be varied from effective to ineffective (Fig. 4). Most centres adopt an approach with the administration of graduated doses between  $1 \times 10^6$  CD3 cells per kg and  $1 \times 10^8$  per kg recipient body weight depending on time from transplant, patient performance status and type of donor.

DLI may also be administered as an adjuvant therapy to chemotherapy or targeted therapies to augment the effect of that treatment or sustain a remission if achieved.

### 12.9.2 Chemotherapy

This may be used to palliate the patient, to attempt to reduce the disease burden to facilitate DLI or targeted therapy or to achieve a remission. Patients relapsing within 6 months of HSCT often require reduced or modified dosing due to the toxicity of previous treatment or having reached the dosing limits of particular chemotherapeutic agents. Regimens for relapsed patients tend to be patient specific, and there are currently very few standardised approaches. The nursing care of these patients has been well documented in previous chapters.

## 12.10 Molecular or Targeted Therapies

Consideration needs to be given to the administration of molecular or targeted therapies to patients who relapse post-HSCT if they are available. Disease-specific monoclonal antibodies, e.g. brentuximab, in some lymphomas; anti-CD33 agents, e.g. gemtuzumab, in myeloid malignancies; and TKIs in BCR-ABL-positive malignancies can have an important role in this setting.

## 12.11 Second HSCT

If a patient experiences a relapse later post-HSCT, consideration may be given to a second HSCT using stem cells either from the original donor or an alternative donor. In malignant disease, usually a second procedure is only feasible when remission has been achieved following successful administration of chemotherapy, a molecular or targeted therapy. The morbidity and mortality associated with a second HSCT is often significant, and the patient and family should be carefully counselled before such an undertaking.

### Conclusion

The treatment of relapsed disease remains challenging, and further research is required to identify new strategies and therapies to

improve the outcome for this group of patients.

The nursing challenges are immense, and the psychological support required is complex and largely falls to the nurse to coordinate and deliver regardless of the subsequent treatment approach. The nursing team will continue to support patients and their families and help them to adjust to the changes ahead. The demands on the team can mean that it is difficult to take the time to reflect and deal with the changing care and focus for the patients. The adjustments and difficulties experienced in caring for the relapse patient need to be matched by a team that continues to support each other.

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