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Stem Cell Transplantation for Indolent Lymphoma. A Reappraisal

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Summary

Allogeneic transplantation is established as a curative treatment for follicular lymphoma, but with considerable short and long-term morbidity and mortality. Data and controversies regarding conditioning regimen, donor source, GVHD prophylaxis, post transplant interventions and approaches to predict and reduce morbidity and mortality are reviewed. Total body irradiation is very effective but toxic and reduced intensity conditioning is often preferred though associated with somewhat higher rates of recurrence. The risk of chronic GVHD and its late sequelae can be markedly reduced by in-vivo T-cell depletion using alemtuzumab but also leads to somewhat higher incidence of disease recurrence. When using such treatment strategies, one can consider prophylactic or preemptive donor lymphocyte infusions or low toxicity medical treatment such as rituximab.

Overall the long term outcomes, particularly survival and current progression free survival of patients undergoing allogeneic transplantation for indolent lymphoma have steadily improved and transplant can now often safely be considered up to the sixth decade of life. Outcomes of unrelated donor transplantation approach those of HLA-identical sibling transplant and even mismatched umbilical cord transplant can be considered in selected patients. The assessment of risks and benefits is aided by the use of various novel tools.

Keywords

indolent lymphoma; allogeneic transplant; conditioning regimens; donor type

It has been almost forty years since allogeneic stem cell transplantation was introduced, initially as a treatment for aggressive hematologic malignancies.¹ Shortly thereafter the first transplantations were also performed for chronic leukemia. They turned out to be curative and transplant became the preferred therapy for CML and remained so until the advent of TKI.² Allo Stem Cell Transplant for lymphoma had a later start with early studies demonstrating lower recurrence rates after allogeneic compared to autologous transplant.^{3;4} Retrospective single institution studies and registry studies provided convincing evidence of the exceptional curative potential of allogeneic SCT in low grade lymphoma.^{5–9,10} The issues that continue to be debated for allogeneic transplant in low grade lymphoma are

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Conflict of interest statement

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similar to those of chronic leukemia patients. Its role continues to shift amid the plethora of ever changing and improving treatment options. This has been the subject of recent reviews and also has been discussed in a consensus expert statement.^{11;12} The current report does not therefore aim to be exhaustive, but rather focuses on areas of challenges and controversy.

Choosing a conditioning regimen – to TBI or not to TBI?

The issue of conditioning regimen intensity has dominated transplant clinical research and care for the past decade. Reduced intensity conditioning is contrasted to TBI based myeloablative conditioning. TBI, initially introduced for its antileukemic activity and immunosuppressive effects long constituted the backbone of allogeneic transplantation.¹ It was recognized almost a century ago that radiation therapy is a peculiarly efficacious therapy for low grade lymphoma and TBI was commonly used in early studies of allogeneic transplant for lymphoma.¹³ Early reports also found that TBI, compared to “other regimens” was associated with improved survival after allogeneic SCT.⁷ But TBI is toxic. Mucositis can be debilitating and is further exacerbated by post transplant methotrexate.¹⁴ Renal, hepatic and particularly pulmonary toxicity are life-threatening and TBI has been used rarely in older patients. Concerns over toxicity led to the development of RIC, using either reduced doses of radiation or none at all. But any reduction in TRM is modest at best. In a registry analysis we failed to show any benefit for RIC but did find a somewhat increased rate of disease recurrence (figure 1).¹⁵ The best evidence of advantages for RIC comes from Seattle studies demonstrating improved survival after non- myeloablative conditioning, but only in those with considerable comorbidities (figure 2).¹⁶ Since many low grade lymphoma patients are older and come to transplant after extensive prior therapy, their comorbidity rates tend to be high. For such pts RIC may be preferable. But for patients who are younger, and lack comorbidities, we continue to recommend TBI- based myeloablative conditioning.

Choosing a donor – What’s in a cord?

Most registry studies of transplant for low grade lymphoma are restricted to recipients of matched sibling transplant, which are available for fewer than half of the patients and which are increasingly problematic as we consider transplant for older individuals and knowledge of the genetic basis of disease increases. We currently estimate that we reject approximately 10 percent of our potential sibling donors because of comorbidities - Older recipients have older and sicker donors.¹⁷ Interestingly, there are also increasingly frequent reports of clonal hemato-lymphopoiesis or genetic lesions in siblings of potential transplant recipients.^{18;19}

Advances in unrelated donor selection including high resolution HLA typing has resulted in major improvements in outcome of unrelated donor transplant.²⁰ In most recent studies, long term outcomes of unrelated donor transplant mirror those of sibling transplantation, though with a somewhat increased incidence of GVHD. Studies focusing on unrelated transplant for indolent lymphoma patients are still limited mostly to older series that predictably have a somewhat worse outcomes.²¹ But many recent large studies have a considerable number of unrelated donor recipients, who appear to have similar or even better outcomes than matched sibling transplants.²² For all practical purposes, most centers consider the risks of HLA identical unrelated donor SCT as equivalent to those of matched sibling SCT.

As donor typing becomes more accurate, it is also increasingly clear that many patients, particularly those of minority descent, lack matching donors.²³ Alternative donor transplant i.e. haplo-identical and/or cord blood transplantation is increasingly considered but published reports on alternative donor transplant for lymphoma remain scarce. We have included several patients with indolent lymphoma in our umbilical cord blood transplant studies with excellent success.

Predicting TRM and morbidity

It is widely accepted that allogeneic transplant is curative, but its widespread acceptance and use has been limited because of concern over treatment related mortality which was strikingly high in early reports. TRM in allo SCT has however decreased considerably over time as shown in a recent publication in the New England Journal of Medicine.²⁴ We showed several years ago in an analysis of myeloablative conditioning for low grade lymphoma, how TRM has decreased over time, probably due to better patient selection and to improved supportive care.²⁵ But even in the best series, TRM of approximately 10 % is usually found and this remains concerning for patients who often have the choice of less toxic palliative approaches. The accurate prediction of risk can be very helpful for individual patients and physicians in the process of deciding on treatment strategies and is currently based on an assessment of patient and disease related factors.

Patient related factors include measurement of performance status (PS) which has been consistently predictive of outcome of transplant outcome, but unfortunately has not been captured in many of the large prospective studies. In addition to PS a lot of attention has focused on the assessment of comorbidities. The presence of multiple comorbidities predisposes to higher TRM. We and others have shown that a combination of performance status and comorbidities provide independent predictive value.^{26;27} By using a combination of performance status and chemotherapy sensitivity one can identify and subgroup of patients with low grade lymphoma who have it treatments related mortality of less than 10% at one year. Vice versa, one can also identify subgroups within extremely high treatments related mortality.

The scoring systems used to measure comorbidities nor the measurement of performance status are very reproducible. In an effort to improve predictive accuracy several biomarkers have been studied. The Dana-Farber group has shown that serum ferritin, an acute phase reactant is a reasonable predictor of treatment related mortality.²⁸ To extrapolate from there that patient should undergo iron removal prior to transplant, is however premature. We and others have investigated serum CRP as a reliable predictor off treatment related mortality.²⁹³⁰⁻³²

Disease-related factors consist of the assessment of disease responsiveness. Those with refractory disease consistently have a higher treatments related mortality (as well as a higher rate of disease recurrence).^{15;33} Radiologic assessment should probably be limited to CT scan; PET scan has a limited role in indolent lymphoma and does not appear to predict outcome of allo transplant for lymphoma in general.^{34;35}

Reducing TRM and morbidity

The most efficacious fashion in which to prevent early ransplant related morbidity and mortality consists of selecting patients in better condition and with well controlled disease, therefore to transplant patients rather early in the course of their disease. The ideal patient is in second remission, has an excellent performance status and a limited number of comorbidities. He or she also has a matched sibling or matched unrelated donor. Transplant in such patients can be offered with a high rate of success and a one year treatment related mortality of approximately 10%. Typically reduced intensity conditioning regimens are utilized with great success and limited early morbidity and mortality.³⁶ The decision to proceed with transplant should then be weighed against other, less treatment options available to such patients. These include autologous stem cell transplant, which may have a cure rate in the 50% to 60% range, as well as a number of novel chemo-immunotherapeutic approaches.

But what to offer the patient whose disease is less well controlled and whose performance status has declined as a consequence of previous attempts at reinduction, and due to the burden of disease?³⁷ Such patient's disease is rarely controlled with RIC transplant, only occasionally with myeloablative conditioning, and they have considerable risk of early treatment related morbidity and mortality.^{38;39} Established treatment alternatives are limited. We tend to refer such patients for participation in studies of novel drug treatments, of which fortunately many are available. Most recently temsirolimus, lenalidomide and even clofarabine have shown activity. Successful cytoreduction will likely cause improvement in performance status and a much better overall outlook for long term success of allogeneic transplantation. Various other transplant approaches are under evaluation. Such patients are also excellent candidates for studies of novel transplant approaches and conditioning regimens.⁴⁰⁻⁴⁴

Many efforts have also been devoted to reducing morbidity and mortality of patients undergoing conditioning. Modifications in conditioning and in drugs for GVHD prevention all may influence the risks for mucositis, renal, or hepatic toxicity.²⁴ Major strides have also been made in diagnosis, prophylaxis, and treatment of viral and fungal infections as well as in transfusion support. All these advances contribute to steady improvement in medium term outcomes of transplantation.

But transplant patients are also at risk for long term complications occurring years and even decades after transplant. These include infertility, early menopause, osteonecrosis, chronic pulmonary and cardiac problems and increased risk for skin cancer.⁴⁵⁻⁴⁸ Transplant patients in remission face an ongoing risk of death that well exceeds that of an age matched population.⁴⁶ This increased risk extends well beyond a decade after transplant. Chronic GVHD and/or its treatment are the major risk factors for many of these late complications, and avoidance of late chronic GVHD underlies our interest and that of other groups in T-cell depleted transplant which, despite a somewhat increased risk of recurrence, may result in better health condition for survivors.

Relapse

The most effective way to conduct an allogeneic transplantation for low grade lymphoma is to use a myeloablative conditioning regimen combined with standard GVHD prophylaxis (cyclosporine-methotrexate). Rates of recurrence are exceedingly low, but treatment related mortality, acute toxicity and chronic illness in survivors constitute serious problems. Reduced intensity conditioning decreases acute toxicity and somewhat reduces mortality but does not address, indeed possibly worsens, issues relating to chronic GVHD. It also is associated with a somewhat increased rate of disease recurrence. T cell depleted SCT, most commonly using alemtuzumab, reduces chronic GVHD and related complications, but may be associated with a further increase in risk for disease recurrence.^{22;34;49;50} Little by little an approach has gained favor in which, despite stated intent at curative therapy, an increased risk of disease recurrence is accepted. The detection and management of disease recurrence therefore takes on additional importance as a topic of research interest. Several strategies have been utilized.

Some groups have used a decline in percentage donor chimerism as a surrogate for disease recurrence and a trigger for preventive intervention, usually with donor lymphocyte infusions. The UK cooperative group in this regard has published interesting results with excellent long term survival outcomes, and has coined the term "current progression-free survival" to describe patients who, with the use DLI and small doses of rituximab have obtained durable subsequent remissions.²²

The measurement of chimerism is however not a standardized test and results depend heavily on the lineage measured, and the body compartment (blood vs marrow) sampled. For example, in our own experience, using a similar conditioning regimen as the UK group, we found that percentage donor chimerism in CD3 cells was often lower than that in unfractionated cells.⁵¹ CD3 chimerism was indicative for risk of GVHD but neither CD3 nor unfractionated chimerism was associated with risk of disease recurrence (With the caveat that only a minority of our patients had lymphoma). Others have also failed to detect an association between chimerism and risk of disease recurrence.⁵² Until better surrogates for disease recurrence are available, we do not recommend prophylactic donor lymphocyte infusion and have described similar results to those reported by the UK group.³⁴

Instead we have focused on the management of patients with clinical (i.e. pathologic or radiologic) evidence of disease progression. Previously we and others showed that such patients may benefit from immune manipulations such as withdrawal of immunosuppressants or donor lymphocyte infusions.^{53;54} Over the past decade we have much more commonly used rituximab, often in combination with chemotherapy to treat patients with disease recurrence. These interventions carry less risk of inducing graft vs host disease and appear equally effective to DLI. Those with recurrences occurring more than 6 months after the transplant commonly achieve prolonged and even durable responses to treatment(figure 3).³⁴ Paradoxically, some of these results are obtained in response to medications to which previously the same patient had transient responses at best (illustrated in figure 4). Since most of the patients at the time of disease recurrence still have persistent blood and marrow donor chimerism, it is likely that GVL effects continue to be operative and contribute to the increased sensitivity to salvage therapy.

Conclusion

Transplant technologies have evolved faster than our ability to prospectively test them for uncommon indications such as indolent lymphomas. As a result, uncertainty surrounds many of the choices facing patients and transplant physician. When in the course of the disease to offer transplant? What type of donor to utilize? What conditioning or GVHD prophylaxis? How to manage or prevent recurrence? –All these are important clinical questions the answer to which is informed by judgment and personal experience as much as by objective data. Overall however, the field of allogeneic transplant is making slow but steady progress; thanks to alternative donor strategies we now have the ability to offer transplant to more patients and outcomes, at least in terms of long term survival and quality of life, have steadily improved. There are many remaining opportunities for improvement. The major challenge may well be how to prioritize and design clinical studies to optimally test novel approaches utilizing a limited patient number.

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CIBMTR Study 3: Adjusted Probability of PFS after Allotx for Follicular Lymphoma by Conditioning Regimen

Hari, BBMT 14:236, 2008

Figure 1.

Comparison of progression free survival after RIC conditioning vs myeloablative conditioning for low grade lymphoma (ref 15)

Seattle: NRM and survival estimates among nonmyeloablative vs myeloablative tx in NHL or CLL

Sorrer, M. L. et al. Blood 2008;111:446-452

Figure 2.

Survival and non-relapse mortality (NRM) after myeloablative vs non-myeloablative transplant for NHL and CLL. Outcomes are similar for those without comorbidities (HCT CI=0) but superior after non-myeloablative transplant for those with comorbidities (HCT CI>1) (ref 16)

Survival after relapse, by time to relapse

Figure 3.
Survival after relapse in lymphoma patients relapsing less than 6 months vs those relapsing more than 6 months after transplant (ref 34)

Salvage chemo-immunotherapy for relapse after allo transplant

- 64 yr old female
- Multiply relapse d lymphoplasmocytic lymphoma.
- Failed Fludara and Rituximab
- Bone Marrow, Spleen involvement
- Allo TX 12/01
 - HLA Identical Sibling
 - Fludara – Mel – Alemtuzumab
 - No GVHD
- 24 months after TX: relapse in BM with thrombocytopenia
- Fludara – Rituxan x4 :
 - Remission >4 years
 - Late 2007: lung CA
- No DLI

36

Figure 4.

Platelet counts in a patient with CD5 negative lymphocytic lymphoma who relapse one year after transplant. She had prior to transplant failed rituximab and fludarabine treatment. At relapse, she had thrombocytopenia as a consequence of extensive bone marrow involvement. Upon further treatment with 4 courses of fludarabine rituximab, she obtained a durable complete remission with normalization of blood counts. No DLI was used and no clinical GVHD was observed.