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Alemtuzumab in allogeneic hematopoietic stem cell transplantation

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Abstract

Introduction—With the use of reduced-intensity conditioning (RIC), early toxicity of allogeneic stem cell transplantation (SCT) has been much reduced. Graft-versus-host disease (GvHD) causes morbidities and mortality. Alemtuzumab is a mAb directed against CD52. When administered prior to transplant it leads to T-cell depletion. Incorporation of alemtuzumab in RIC results in low rates of GvHD and treatment-related mortality (TRM) in haematological diseases, even in the setting of mismatched-donor transplantation.

Areas covered—The use of alemtuzumab for GvHD in SCT. The benefit of alemtuzumab-based conditioning is partially offset by increased disease relapse due to impaired graft-versus-tumor effect (GvT) and by slower immune reconstitution, necessitating special precautions. While GvHD is prevented with alemtuzumab, post-SCT interventions are often required. Most studies find that alemtuzumab-based conditioning results in decreased chronic GvHD and TRM, but also in decreased progression-free survival. Overall survival after 3 – 5 years is usually equivalent and quality of life may be improved because of a lower incidence of sequelae of chronic GvHD. Many aspects of alemtuzumab treatment are under investigation.

Expert opinion—Alemtuzumab reduces GvHD and TRM after SCT. Use of alemtuzumab requires awareness and strict management of the risk of opportunistic infections and of an increased risk of disease recurrence.

Keywords

alemtuzumab; allogeneic stem cell transplantation; graft-versus-host disease; T-cell depletion

1. Introduction

Allogeneic hematopoietic stem cell transplantation (SCT) is an important treatment option for haematological malignancies as well as for some non-malignant diseases, but carries a considerable risk for complications that are life-threatening and/or affect quality of life. In recent decades, improvements in conditioning regimens and supportive care have resulted in steady reduction of treatment related mortality (TRM) [1] but graft-versus-host disease (GvHD) remains a problem [2], and has become even more prominent in the era of reduced-

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intensity conditioning (RIC) which relies on graft-versus-tumor (GvT) effects to achieve tumor response. Acute GvHD usually occurs within the first months after transplant and affects mainly the skin, gastrointestinal tract and liver. It occurs in 25% – 70% of patients, depending on the type of donor and conditioning. Chronic GvHD, which has distinct clinical features and tends to develop later occurs in 30% – 50% of patients and is the leading cause of late mortality after SCT [2,3]. GvHD physiopathology is complex but is mediated to a large extent by alloreactive donor T-cells [4]. All stem cell transplants require GvHD prophylaxis, usually based on blocking of T-cell function with calcineurin inhibitors [5]. An alternative and more efficient method of GvHD prophylaxis consists of the removal of donor T-cells *in vitro* through physical methods [6], the use of anti-lymphocyte antibodies [7] or column-based immunomagnetic selection of specific cell populations [8]. Lastly, GvHD can be prevented by *in vivo* administration of antibodies that lyse lymphocytes, in particular alemtuzumab or anti-thymocyte globulin (ATG).

Alemtuzumab is a humanized anti-CD52 monoclonal antibody, which effectively depletes both B and T cells from circulating blood with limited or no effect on hematopoietic progenitors [9]. The first anti-CD52 antibody was developed in the Cambridge Pathology-1 lab (CAMPATH-1) as a tool to deplete donor T-cells before SCT [4]. The original CAMPATH molecules were rat-derived antibodies and included an IgM antibody (CAMPATH-1M), and subsequently an IgG antibody (CAMPATH-1G) both of which were studied for *in vitro* and *in vivo* T-cell depletion respectively. Both caused significant reduction in GvHD [7], but their benefit was offset by an increased risk of graft rejection caused by residual host T-cells and an increased risk of relapse due to the impaired GvT effect [7]. Subsequently, a humanized antibody was engineered (CAMPATH-1H or Alemtuzumab) to decrease immunogenicity and for myriad clinical applications [4]. It has potent activity in chronic lymphocytic leukemia (CLL), and is approved for CLL therapy [9]. It also has unique activity in various T-cell lymphomas in particularly in T-prolymphocytic leukemia (T-PLL) [10]. It is used for treatment of severe aplastic anemia (AA) [11] and has shown remarkable benefit in multiple sclerosis [12]. In organ transplantation, alemtuzumab has shown promising results in tolerance induction [13–16]. Alemtuzumab also continues to be widely used in many countries as a very effective method for prevention of acute and especially chronic GvHD after transplantation that is widely used in the United Kingdom and in many other centers around the world [2,17,18].

Relapse and delayed immune reconstitution remain concerns of this method and are the reasons why its application in SCT is not universally accepted [2]. Small series have also reported its role in acute GvHD therapy [19]. In this review, we provide an overview of the current role and recent data on alemtuzumab in SCT.

2. Structure and mechanism of action

Alemtuzumab is a recombinant humanized monoclonal IgG1 antibody directed against the CD52 antigen, a 12 amino acid, 28,000 molecular weight glycosylated glycosylphosphatidylinositol (GPI)-linked cell surface protein [20]. The function of CD52 remains largely unknown but it is expressed on more than 95% of peripheral blood lymphocytes, monocytes, eosinophils and macrophages and on some dendritic cells but not on granulocytes, red blood cells, platelets or hematopoietic progenitor cells [21–23]. It is also expressed in the male reproductive tract where CD52 is necessary for spermatozoa to preserve normal motility [24]. CD52 antigen density is higher on normal T lymphocytes than on normal B lymphocytes, a pattern of expression recapitulated on T and B neoplasms [21,22]. Differences in CD52 expression may explain differential sensitivity to alemtuzumab *in vitro* and *in vivo*. Indeed, alemtuzumab depletes peripheral B and T cells effectively but the pattern of recovery varies among the different subsets. Memory T cells are partially

spared by alemtuzumab [14] while CD8⁺ cells recover more rapidly than CD4⁺ cells [16,25,26]. NK cells are effectively depleted by alemtuzumab but tend to recover rapidly after SCT [25,27]. Alemtuzumab also removes monocyte-derived dendritic cells from the circulation. This decreases phagocytosis and presentation of host-derived antigens which probably contributes to further reduction in GvHD early after SCT [28]. Most of the CD52 is membrane bound, but in CLL, a disease characterized by high expression of CD52 on the tumor cells, some of the antigen is shed. As a result, soluble CD52 can readily be detected in the plasma of patients with CLL and may modulate response to alemtuzumab *in vivo* [24].

The mechanism by which alemtuzumab mediates lympholysis is complex and includes complement-mediated cell lysis (complement-dependent cytotoxicity (CDC)), antibody-dependent cellular cytotoxicity (ADCC) and direct apoptosis [29]. Depending on experimental conditions, *in vitro* studies have found a prominent effect of the complement pathway [30], a strong ADCC through a caspase-dependent pathway [31] or a direct caspase-independent apoptotic pathway [32]. In a human CD52-transgenic mouse a major role for ADCC in lymphocyte depletion has been shown, with neutrophils and NK cells as potential effectors [26,33]. However, high-affinity IgG Fc receptor (FCGR) polymorphisms are not correlated with clinical response to alemtuzumab in CLL, suggesting that *in vivo* its mechanism of action is not limited to ADCC [34].

3. Pharmacology and dosing of alemtuzumab in transplant protocols

The incorporation of alemtuzumab in transplant protocols has a dual purpose, namely reduction in GvHD (both acute and chronic) and the prevention of graft rejection. Its major side-effects are immune suppression, resulting in opportunistic infections and increased risk for recurrence because of reduction in GvT effects. The dosing schedule of alemtuzumab with optimal efficacy and minimal side-effects has been the subject of much empirical research.

In many transplant protocols, alemtuzumab is administered intravenously during conditioning similar to the original CAMPATH-1G though alemtuzumab has slower clearance than CAMPATH-1G and is therefore a more potent immunosuppressant [35]. It is practically always combined with single agent post-transplant prophylaxis consisting of a calcineurin inhibitor (cyclosporin A or tacrolimus). Post-transplant methotrexate is not usually administered in these protocols and this accounts for a low incidence of mucositis. Alemtuzumab clearance depends on the actual dose administered, the total number of CD52 binding sites, the hepatic function and also the monocyte–macrophage system. In practice though, most centers have used fixed dose-schedules of alemtuzumab. After the commonly used schedule of alemtuzumab 20 mg daily for five days (total 100 mg), a median absolute lymphocyte CD4⁺ level higher than $200 \times 10^6/l$ was not reached until 9 months after SCT. The terminal half-life of alemtuzumab was 8 days and time to achieve levels below 0.1 µg/ml was estimated at 60 days. Concentrations as low as 0.1 µg/ml are sufficient for ADCC and therefore ongoing lymphocyte depletion might occur for approximately 2 months after SCT [36].

Based on concerns for impaired immune reconstitution and GvT effect, some investigators have attempted to lower the dose of alemtuzumab. Tholouli *et al.* reported 98 acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients who received either 50 or 100 mg alemtuzumab as part of RIC. Except for a trend for lower relapse with 50 mg, no differences were observed in terms of overall survival (OS), TRM and cytomegalovirus (CMV) reactivation [37]. Alemtuzumab doses as low as 10 mg may result in prolonged lymphopenia [38] and hence even lower doses have been explored. Bertz *et al.* reported that further de-escalation of *in vivo* alemtuzumab to 10 – 20 mg total dose given on day –1 was

safe. There were no increases in severe acute and chronic GvHD or graft failure. There also did not seem to be an effect on relapse [39]. These data were confirmed by Spyridonidis *et al.* in a small study of 18 patients who received 10 mg alemtuzumab before sibling and matched unrelated SCT [40]. Chakraverty *et al.* also demonstrated that dose reduction of alemtuzumab to 30 mg given on day -1 effectively prevents GvHD and is associated with more rapid lymphocyte recovery after HLA-identical sibling SCT [41]. In their experience however, a dose of 20 mg or lower was associated with incomplete saturation of CD52 binding sites, more rapid clearance and greater risk of severe acute and chronic GvHD. In general, a dose of 30 mg or lower is associated with a significant fall in alemtuzumab level by day 28. Others reported concerns about increased incidence of Epstein-Barr virus (EBV)-driven post-transplant lymphoproliferative disease (PTLD) following a reduction in alemtuzumab total dose from 50 to 30 mg. Low-dose alemtuzumab may be insufficient to deplete B cells, allowing EBV-infected B cells to survive and potentially lead to PTLD [42]. In summary, the standard total dose of 100 mg seems more than is required in most transplant settings. Doses of less than 30 mg may be insufficient and predispose to increased risks of GVHD and of PTLD.

Biodistribution and clearance of alemtuzumab are further influenced by a high burden of CD52 antigen on active tumor, or soluble CD52 circulating in the bloodstream [43]. This has implications for transplant in highly CD52-positive neoplasms, particularly CLL. Presence of residual disease at the time of transplantation increases antigen concentration and shortens alemtuzumab plasma half-life. In this setting, the standard dose of alemtuzumab used in RIC might be insufficient to prevent graft rejection and GvHD [44,45]. Indeed, Delgado *et al.* reported a high incidence of graft failure (15%) after alemtuzumab-based RIC in CLL patients [46].

Subcutaneous (SQ) alemtuzumab has gained widespread usage in the treatment of CLL because it is associated with fewer infusion-related side effects and similar pharmacology [43]. Juliusson *et al.* administered SQ alemtuzumab at a dose of 30 mg $\times$ 3 to 26 patients and as a single dose of 30 mg to 14 patients. Immediate toxicity was minimal, and the lower dose of alemtuzumab was associated with low incidence of GvHD and excellent immune recovery [47].

Some groups, instead of administering alemtuzumab *in vivo*, have added it to the stem cell infusate at a usual dose of 20 mg (so-called 'Campath in the bag') [48,49]. This results in lysis of donor lymphocytes in the infusate. Since the product is infused without further manipulation, some of the alemtuzumab is also administered to the recipient and results in host immunosuppression [50]. This simple technique has been associated with a low incidence of both acute and chronic GvHD and low TRM [50–53]. Immune reconstitution remains an issue and some investigators have decreased the dose to 10 mg or 1 mg/10¹⁰ mononuclear cells with similar GvHD prophylaxis but fewer infectious complications [52,53]. The issue of graft rejection reported in the initial studies of Campath-1M, is no longer of much concern, because of the longer half-life of alemtuzumab, which persists for some time in the recipient, a higher stem cell dose and a more potent immunosuppression of the recipient with fludarabine [52].

4. Clinical efficacy in allogeneic transplant for hematologic malignancies and related disorders

The most consistent benefit of alemtuzumab-containing conditioning regimens is the effective and dramatic reduction in acute and chronic GvHD and consequently low TRM [2,7,17]. While other RIC SCT report a 40% – 60% incidence of grade II – IV acute GvHD, most studies of alemtuzumab-containing regimens have observed an incidence of 10 to 20%

acute GvHD, a low incidence of extensive chronic GvHD and a TRM of 10% – 20% [2,17,18]. The reduction in GvHD also applies to unrelated donor transplant [17,18]. Mead *et al.*, in a large retrospective study report that alemtuzumab may overcome the adverse effect of HLA mismatch and an 8 – 9/10 HLA-mismatched unrelated donor may be a reasonable option in this setting [54]. Alemtuzumab has also been administered after RIC haplo-identical SCT with very low rates of GvHD (16%) [55] but long-term outcomes remain disappointing [56]. Results from selected studies are reported in Tables 1 and 2.

Early on, it was observed that the efficacy of alemtuzumab in preventing GvHD was associated with a higher rate of mixed chimerism and a higher rate of disease recurrence [7]. The balance between increased risk of disease recurrence and decreased GvHD determines the overall utility of alemtuzumab-based conditioning in the various diseases that are discussed below.

AML and MDS can be cured with SCT but myeloablative conditioning is restricted to younger patients because of excess TRM and GvHD in older patients. Various RIC have been tested in older patients without a consensus on conditioning or GvHD prophylaxis. Studies using an alemtuzumab-based RIC SCT have TRM from 15% to 25% (Table 1) and have a very low incidence of severe acute and chronic GvHD [57–62]. We reported our own experience with 95 AML/MDS patients and compared them with 59 patients who received identical conditioning without alemtuzumab. Acute GvHD (23% grade II – IV) and especially chronic GvHD (16%) were effectively reduced by the addition of alemtuzumab. We found a non-significant increase in recurrence rates (24%) with alemtuzumab, and a non-significant decrease in TRM (25%). OS was nearly identical between both groups [59,60]. Another recent comparison between alemtuzumab and no alemtuzumab has been reported by Malladi *et al.* They found a trend toward less severe acute GvHD (14%) but a significant reduction in extensive chronic GvHD (4%) for alemtuzumab patients. There were no significant differences in non-relapse mortality and relapse risk between both groups [63]. Outcomes were significantly correlated with active disease at the time of transplant, adverse risk cytogenetics and increased intensity of post-transplant immunosuppression [64]. Collectively, alemtuzumab-based RIC is of interest in patients with AML and MDS due to its strong effect on extensive chronic GvHD. Relapse may be slightly increased, but this drawback is more than offset by a modest reduction in TRM and a major reduction in GvHD-related morbidity.

CD52 is also expressed on 66% – 78% of acute lymphoblastic leukemia (ALL) cells and alemtuzumab as part of the conditioning offers the dual benefit of reduced GvHD with a potential anti-leukemia effect. Primary results in a small cohort of 48 patients are encouraging [65].

Subgroups of patients with aggressive non-Hodgkin's Lymphoma (NHL) are considered routinely for allogeneic transplant. This includes those who have refractory disease or patients relapsing after autologous transplantation. Myeloablative SCT in this setting is associated with very high TRM [66]. RIC may have advantages particularly in patients with comorbidities, but has considerable rates of disease recurrence. The incorporation of alemtuzumab in RIC result in significantly lower rates of acute (10% – 17% grade II – IV) and chronic GvHD (7% – 18%) but similar overall survival (Table 2), which is determined mainly by the disease status and patient's condition [46,67–72]. Similar to aggressive NHL, SCT for Hodgkin's lymphoma (HL) is mainly used for failure of autologous SCT and is also associated with very high TRM using standard conditioning. Alemtuzumab-based RIC has low TRM (16%) and has shown very promising results in this situation, particularly for those with chemosensitive relapse [73–75]. SCT may have a more important role in those lymphoproliferative disorders that have frequent bone marrow involvement including mantle

cell lymphoma, follicular lymphoma and CLL. Follicular lymphoma has a very low rate of recurrence after myeloablative allogeneic transplant. This favorable outcome is variously attributed to GvT effects or to the combination of myeloablative conditioning with the infusion of a tumor-free graft [76]. RIC conditioning has less regimen-related toxicity, but increased complications due to GvHD, resulting in overall nearly similar TRM. Alemtuzumab-containing conditioning has shown a low incidence of GvHD, low TRM and excellent long term survival [17,67,70,77]. Some of the best results were reported by Faulkner *et al.* who used a bis-chloroethylnitrosourea, etoposide, Ara-C, melphalan (BEAM)-alemtuzumab conditioning with low rates of TRM (8%) and GvHD (17%) [78,79]. After the more commonly used fludarabine-melphalan conditioning, late recurrence is frequent but can often be successfully managed by donor lymphocyte infusions (DLI) or low intensity chemo-immunotherapy [70,77]. Similar observations apply to mantle cell lymphoma (MCL), where a high relapse rate was observed but DLI induced a significant number of sustained responses [69].

The role of alemtuzumab in conditioning for chronic leukemias or in myeloma is more controversial. In CLL, a higher rate of graft failure was observed with alemtuzumab-based RIC, and a higher TRM (26%) related to frequent and fatal infections [46]. Profound pre-existing immunosuppression in patients with advanced CLL may contribute to the higher complication rates [46]. In one series, patients receiving alemtuzumab-based conditioning had worse long-term survival. The small number of such patients and the non-random assignment of patients to particular conditioning regimens in this study precluded firm conclusions on the role of alemtuzumab in the poor outcomes [80]. In chronic myelogenous leukemia (CML), addition of alemtuzumab was associated with a higher relapse rate [81] but these recurrences can be effectively salvaged with DLI and/or tyrosine kinase inhibitors (TKI). Results in advanced-phase CML were disappointing [82]. In multiple myeloma (MM), a large retrospective study from Crawley *et al.* identifies alemtuzumab as a predictor for reduced chronic GvHD but also increased relapse rate [83]. Progression-free survival was reduced in patients receiving alemtuzumab-based conditioning, but OS was not.

In severe aplastic anemia, graft rejection and chronic GvHD are major obstacles to successful outcome after SCT. Alemtuzumab can effectively reduce GvHD with low rate of graft rejection [84]. Sickle cell anemia is another non-malignant disease where SCT may provide long-term survival. GvHD is particularly unwelcome in this situation and alemtuzumab has been successfully incorporated in RIC [85]. Finally, graft failure is a rare complication after SCT but carries a dismal prognosis. Risk factors for graft failure include HLA-mismatch, T-cell depletion, alloimmunization, RIC and poor graft quality [86]. Alemtuzumab associated with fludarabine induces substantial immunosuppression allowing second transplant with high engraftment rate and minimal toxicity [87].

Alemtuzumab may also have a role in the management of acute and chronic GvHD, though only small studies and preliminary results have been reported. Different schedules and doses have been used with a response observed in 55% – 78% of patients and complete response in 33% – 35%. The best responses were observed in gastrointestinal GVHD. As expected, infectious complications were common with invasive aspergillosis and CMV reactivation the most frequent. Lower doses of alemtuzumab (3 – 10 mg every 14 days) may be sufficient for GvHD therapy and have fewer infectious complications [19,88,89]. Reports on the use of alemtuzumab in chronic GvHD are even more anecdotal [90].

5. The role of salvage therapy and donor lymphocyte infusion to prevent or treat recurrence in alemtuzumab-based conditioning

T-cell depletion in general, including that mediated by alemtuzumab, has been recognized for many years as a risk factor for disease recurrence after SCT [5] which is usually managed with further chemotherapy and/or DLI. DLI can induce remissions through mediation of a GvT effect, but carries the risk of aplasia and GvHD, only partially prevented by dose reduction of DLI [91,92]. Responses to DLI have been reported in different diseases but while very good response rates are observed in indolent NHL and chronic-phase CML, efficacy is limited in acute leukemia or aggressive NHL [46,61,67–70,73]. Other therapeutic approaches such as reinduction chemotherapy in AML [93], TKIs in CML [82] or chemo-immunotherapy in NHL [77] are also often remarkably effective and can induce prolonged responses. The ability to effectively salvage patients after relapse distinguishes alemtuzumab-based conditioning from other RIC transplants and explains the observation that in many analyses alemtuzumab predisposes for recurrence, but not for decreased overall survival. 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 lymphoma patients who experienced relapse after SCT but who, with DLI and small doses of rituximab obtained durable subsequent remissions [70]. In the calculation of ‘current progression-free survival’, requirement for DLI is not considered a censoring event.

Mixed T-cell chimerism is frequent after alemtuzumab-based RIC and has been associated with tolerance induction and with less GvHD. Some groups have used mixed chimerism as an indicator for imminent disease progression and have administered prophylactic DLI to such patients [17,62,75]. This has frequently resulted in full donor chimerism, and such patients have done well. Conversion to full donor chimerism has been postulated as an effective means to decrease relapse and to obtain prolonged disease control [70,75]. The studies were, however, not conducted in a prospective fashion and, selection and attrition bias may have played a major role in the outcome of those receiving prophylactic DLI [92]. Somewhat surprisingly in one study of Hodgkin’s lymphoma [75], recurrence rates were lower in those receiving prophylactic DLI for mixed chimerism than in those who were fully chimeric and who did not receive DLI [75]. Others, including our own group, have found that stable mixed chimerism is not a predictor for relapse and is possibly associated with better outcome because it predicts for less GvHD [62]. By contrast, a decline of more than 15% in T-cell chimerism between day 30 and day 180 predicted disease recurrence [94]. Close monitoring of full and T-cell chimerism is then mandatory to help guide therapeutic intervention after alemtuzumab-based RIC.

6. ATG versus Alemtuzumab

ATG is the other effective agent for *in vivo* T-cell depletion. Several formulations of ATG are available. They are polyclonal rabbit or horse immunoglobulins directed against multiple human lymphocyte cell-surface antigens. ATG binds to T-cells resulting in T-cell depletion via opsonisation and lysis following complement activation [95]. There may be considerable differences between the various ATG formulations (Thymoglobulin, ATG-Fresenius and ATGAM) but they are all polyclonal products directed against T-cells, in contrast to alemtuzumab which is a monoclonal antibody that depletes both T-and B-cells. Both ATG and alemtuzumab allow rapid engraftment and reduce GvHD effectively but the relative merits of these agents remain a matter of debate and ongoing study. In a comparative study in myeloma, alemtuzumab was associated with a lower rate of complete remission and a higher incidence of CMV reactivation than with ATG. No difference in relapse was found [96]. Juliusson *et al.* replaced prospectively ATG with alemtuzumab given subcutaneously

for 3 days in their RIC protocol. They showed an attractive short-term toxicity profile for alemtuzumab but with slower lymphocyte recovery and with more mixed chimerism. The greater need for DLI and the higher incidence of opportunistic and fatal infections resulted in an impaired OS compared with ATG. They subsequently changed their protocol to one day alemtuzumab (30 mg) given on day -5 which translated into the same OS but with less toxicity than with ATG [47]. In a small retrospective study, Norlin *et al.* showed that alemtuzumab was associated with less overall acute GvHD but more chronic GvHD than ATG. Nevertheless, similar OS, relapse-free survival and infections rate were observed [97]. Finally, the International Bone Marrow Transplantation Registry (IBMTR) reported a large analysis comparing alemtuzumab, ATG and T-cell-repleted RIC transplants. Despite a significant reduction of both acute and chronic GvHD, T-cell depletion was associated with lower disease-free survival. The lowest OS was observed with ATG [98]. Possibly the most important advantage of alemtuzumab over ATG is the relatively low risk of EBV PTLN associated with alemtuzumab exposure [99] due to the effective B cell depletion by alemtuzumab. The respective effect on long term incidence of GvHD, relapse and survival of ATG versus alemtuzumab will require further prospective study.

7. Safety

Alemtuzumab is generally well tolerated with immediate toxicity mainly related to first-dose reactions, including fever, rigor and skin rash. Those reactions decrease with subsequent dosing by administering pre-treatment antihistamines and acetaminophen, and by slowing the rate of injection [29]. Interestingly, the first dose of alemtuzumab in transplant conditioning is usually administered as a full dose of 20 mg, with steroid prophylaxis, in contrast to the dose-escalation schemes often followed in CLL treatment. The subcutaneous route is associated with a better safety profile but rarely used in transplant [43]. A major concern with the use of alemtuzumab is the impaired immune reconstitution. Lymphopenia is often prolonged. CD4⁺ cell recovery is very slow, while CD8⁺ and particularly NK cells increase more rapidly [100,101]. This prolonged immunosuppression leads to an increased risk of opportunistic infections and requires close monitoring. CMV reactivation is very common and occurs early after SCT [102]. CMV reactivation has been observed in 30% to 85% of patients in different studies but CMV disease remains rare due to an effective pre-emptive strategy [2,17,46,57–59,62,67–70,73]. Because of a relative rapid CD8⁺ cell recovery, CMV-specific T-cells increase after episodes of CMV reactivation [103]. In combination with PCR-based detection of CMV DNA and prompt ganciclovir and/or valganciclovir therapy, most CMV reactivation remains self-limited [104]. At The University of Chicago, we use a very aggressive prophylactic strategy to prevent CMV reactivation. All high-risk patients receive ganciclovir (5 mg/kg intravenously twice daily from day -7 until day -2), acyclovir (500 mg/m² every 8 hours intravenously from day -2 until engraftment) followed by high dose oral valganciclovir (2 g four times daily until day +210). With this well-tolerated strategy, CMV reactivation was decreased to 29% [105]. Beside CMV infection, we have also screened our patients for BK virus and did not find a higher incidence in patients receiving alemtuzumab [106]. Incorporation of alemtuzumab in RIC has also been associated with an increased incidence in EBV infection but low risk of PTLN due to an effective preemptive therapy with rituximab but also due to an effective depletion of B cells with alemtuzumab [42,107,108]. Finally, T-cell depletion with alemtuzumab is a recognized risk factor for adenovirus infections after SCT, particularly in children [109].

8. Conclusion

Alemtuzumab is a well-tolerated and effective drug when used for T-cell depletion before SCT. Its application in RIC results in a significant reduction of both acute and chronic

GvHD and lower TRM. Graft rejection, a considerable problem in studies of earlier CAMPATH products, no longer represents much of an issue with alemtuzumab. *In vivo* administration may actually have graft-enhancing properties. Alemtuzumab has a prolonged half-life, but its pharmacokinetics is influenced by CD52 density on target cells, residual CD52 positive disease and circulating soluble CD52. The customary dosage of 100 mg of alemtuzumab given over 5 days prior to SCT induces profound and prolonged lymphopenia and may be excessive. Lower doses of alemtuzumab provide similar GvHD prophylaxis and may allow better immune reconstitution. However, low-dose alemtuzumab might be insufficient to prevent graft failure and GvHD in CLL patients. Further clinical trials are needed to address alemtuzumab dosage in different settings. Efficacy has been proven in various malignant and non-malignant diseases with GvHD in 10% – 20% and TRM as low as 10% – 20%. The incidence of recurrence and the overall outcome depends on the underlying disease. The long-term results are encouraging in patients with acute leukemia and lymphoma where survival parallels that achieved with other transplant approaches, but with less chronic GvHD. In multiple myeloma and particularly in CLL, high recurrence rates and high rates of opportunistic infections lead to caution in the routine use of alemtuzumab. Regardless of the underlying disease, recurrence is somewhat higher than with other approaches but may often be managed successfully with a variety of salvage approaches, including DLI. Strict surveillance for CMV accompanied by prophylaxis or early preemptive therapy can prevent severe CMV-related complications. Adenovirus infections may be particularly common in children. Other opportunistic infections are in our experience not more common than with conventional GvHD prophylaxis. On the contrary, because of the low incidence of GvHD, the overall incidence of opportunistic infections may actually be reduced. Alemtuzumab is also being investigated for treatment of refractory GvHD.

9. Expert Opinion

Alemtuzumab is a safe and effective drug that can reduce both GvHD and TRM after transplant. The side-effects are an increased risk of disease recurrence and of opportunistic infections, particularly CMV reactivation. The optimal dose of alemtuzumab, which minimizes immunosuppression but maintains effective GvHD prophylaxis, is still under investigation but is probably in the range of 30 – 50mg. Successful use of alemtuzumab containing conditioning regimens requires strict management of CMV viremia and rapid intervention to salvage patients after relapse. Early use of DLI or relatively non-toxic drugs (e.g. TKIs in CML, rituximab or nucleoside analogs in NHL) can be used either for early intervention or, when appropriate, as consolidation. Opportunistic infections may be prevented with adequate prophylaxis or pre-emptive therapy. The *ex vivo* expansion of infection-specific T-cells to support immune reconstitution after T-cell-depleted SCT is also under active investigation.

Glossary

AA	aplastic anemia
ADCC	antibody-dependent cellular cytotoxicity
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ATG	anti-thymocyte globulin
BEAM	bis-chloroethylnitrosourea, Etoposide, Ara-C, Melphalan
CDC	complement-dependent cytotoxicity

CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia
CMV	cytomegalovirus
DLI	donor lymphocytes infusion
EBV	Epstein-Barr virus
FCGR	IgG Fc receptor
GvHD	graft-versus-host disease
GvT	graft-versus-tumor
HL	Hodgkin's lymphoma
HLA	human leucocyte antigen
IBMTR	International Bone Marrow Transplantation Registry
MCL	Mantle cell lymphoma
MDS	myelodysplastic syndrome
MM	multiple myeloma
NHL	non-Hodgkin's lymphoma
OS	overall survival
PTLD	post-transplant lymphoproliferative disease
RIC	reduced-intensity conditioning
SCT	allogeneic stem cell transplantation
SQ	subcutaneous
TKI	tyrosine kinase inhibitor
T-PLL	T-prolymphocytic leukemia
TRM	treatment-related mortality

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Drug Summary Box

Drug Name : Alemtuzumab
Indication under discussion : T-cell depletion to prevent both acute and chronic graft-versus-host disease
Mechanism of action : CD52 ⁺ cells lysis (T and B cells) through CDC, ADCC and direct apoptosis
Route of administration : Intravenous or subcutaneous
Pivotal trials : Kottaridis <i>et al.</i> 2000 [18]; Chakraverty <i>et al.</i> 2002 [17], Perez-Simon <i>et al.</i> 2002 [2] and van Besien <i>et al.</i> 2005 [59]; These large trials described significant efficacy of alemtuzumab as GvHD prophylaxis after RIC SCT in different haematological diseases.

Table 1
Studies on Alemtuzumab-based RIC SCT in unselected diseases and AML/MDS

Study	Diagnosis	Nr	Disease Status	Age	Conditioning	Campath Dose	% Sib	TRM	Grade III – IV aGvHD	Extensive cGvHD	OS	DFS/PFS	DLI
[18]	All	44	39% CR	18 – 56	Flu-Mel	100 mg	82%	11%	No grade III – IV	Not extensive	1y-73%	1y-71%	Only for relapse
[17]	All	47	34% CR	18 – 62	Flu-Mel	100 mg	0%	19.8%	6.4%	Not extensive	1y-75%	1y-61.5%	6/47
[2]	All	78	20% CR	44	Flu-Mel	100 mg	100%	10.2%	2.6%	1/78	1y-72%	1y-76%	18/78
[50]	All	73	-	19 – 61	Cy-TBI	20 mg in the bag	100%	8%	No grade III – IV	13/73	5y-48%	5y-43%	37/73
[54]	All	157	79% S	48	Flu-Mel	100 mg	0%	27%	3%	11.5%	3y-52%	-	44/157
[57]	AML/MDS	62	56% CR	53	Flu-Bu	100 mg	39%	15%	9%	2/62	2y-74%	2y-62%	26/62
[58]	AML/MDS	76	55% CR	52	Flu-Mel	50 – 100 mg	46%	19%	No grade III – IV	2/76	3y-41%	3y-37%	9/76
[59]	AML/MDS	95	50% CR	54	Flu-Mel	100 mg	50%	24.6%	8.6%	16% both limited and extensive	2y-40.5%	2y-33%	No
[62]	AML/MDS	110	51% CR1	53	Flu-Bu	100 mg	33%	21%	10.9%	16%	2y-59%	2y-57%	39/110
[63]	AML	51	94% CR	51	Flu-Mel, Flu-Bu, Flu-Cy	30 – 100 mg	100%	12%	14% grade II – IV	4%	5y-60%	-	-

Age: median age or range, aGvHD: cumulative incidence of grade III-IV acute graft-versus-host disease, All: unselected hematological malignancies, AML: acute myelogenous leukemia, Bu: busulfan, Campath dose: cumulative dose of alemtuzumab, cGvHD: cumulative incidence of extensive chronic graft-versus-host disease, CR: complete remission, CR1: acute leukemia in first remission, Cy: cyclophosphamide, DFS: disease-free survival, Disease Status: disease status at the time of transplantation, DLI: donor lymphocyte infusion given for relapse or mixed chimerism, Flu: Fludarabine, Mel: melphalan, MDS: myelodysplastic syndrome, OS: overall survival, Nr: numbers of patients, PFS: progression-free survival, RIC: reduced-intensity conditioning, S: chemosensitive disease, SCT: allogeneic stem cell transplantation, % Sib: proportion of sibling donors, TBI: total body irradiation, TRM: treatment-related mortality 1 year after transplantation

Table 2

Major studies on alemtuzumab-based RIC SCT in lymphoproliferative diseases

Study	Diagnosis	Nr	Disease status	Age	Conditioning	Campath Dose	% Sib	TRM	Grade III – IV aGvHD	Extensive cGvHD	OS	DFS/PFS	DLI
[67]	NHL	88	88.6% S	48	Flu-Mel	100 mg	71%	23%	4.5%	4.5%	3y-55%	3y-50%	36/88
[68]	HG-NHL	48	83% S	46	Flu-Mel	20 – 100 mg	62%	29%	4.2%	13%	4y-47%	4y-48%	12/48
[77]	NHL, HL	67	66% S	54	Flu-Mel, Clo-Mel, Flu-Bu	100 mg	57%	30%	16.4% grade II – IV	7/67	3y-47%	3y-30%	3/67
[69]	MCL	70	81% S	48	Flu-Mel, BEAM, Flu-Bu	30 – 100 mg	60%	18%	10%	34%	5y-37%	5y-14%	27/70
[46]	CLL	41	83% S	54	Flu-Mel	40 – 100 mg	58%	26%	10%	4.9%	2y-51%	5y-45%	18/41
[70]	FL	82	90% S	45	Flu-Mel	20 – 100 mg	46%	12%	13% grade II – IV	20%	4y-76%	4y-76%	41/82
[79]	FL	44	90.9% S	48	BEAM	50 – 100 mg	64%	20%	No grade III – IV	6.8%	3y-69%	3y-58%	13/44
[78]	NHL, CLL, HL	65	20% CR	46	BEAM	50 – 100 mg	87%	13%	No grade III – IV	No extensive	3y-63%	3y-54%	17/65
[73]	HL	36	55.5% S	36	Flu-Mel	50 – 100 mg	100%	7%	No grade III – IV	2/36	4y-62%	4y-39%	19/36

Age: median age, aGvHD: cumulative incidence of grade III-IV acute graft-versus-host disease, BEAM: bis-chloroethylnitrosourea, Etoposide, Ara-C, Melphalan, Bu: busulfan, Camp: campath/alemtuzumab, Camp dose: cumulative dose of alemtuzumab, cGvHD: cumulative incidence of extensive chronic graft-versus-host disease, CLL: chronic lymphocytic leukemia, CR: complete remission, DFS: disease-free survival, Disease Status: disease status at the time of transplantation, DLI: donor lymphocyte infusion given for relapse or mixed chimerism, FL: follicular lymphoma, Flu: Fludarabine, HG-NHL: High-grade non-Hodgkin's lymphoma, HL: Hodgkin's lymphoma, MCL: mantle cell lymphoma, Mel: melphalan, NHL: non-Hodgkin's lymphoma, Nr: numbers of patients, OS: overall survival, PFS: progression-free survival, RIC: reduced-intensity conditioning, S: chemosensitive disease, SCT: allogeneic stem cell transplantation, % Sib: proportion of sibling donor, TRM: treatment-related mortality 1 year after transplantation