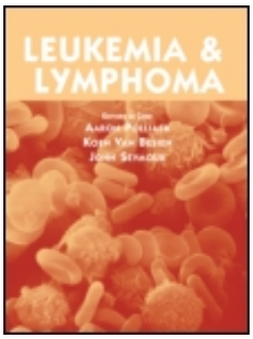

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

Sirolimus plus calcineurin inhibitors and methotrexate: is more necessarily better?

Basem M. William & Marcos de Lima

To cite this article: Basem M. William & Marcos de Lima (2015) Sirolimus plus calcineurin inhibitors and methotrexate: is more necessarily better?, Leukemia & Lymphoma, 56:3, 555-556, DOI: 10.3109/10428194.2014.949262

To link to this article: https://doi.org/10.3109/10428194.2014.949262

Leukemia & Lymphoma, March 2015; 56(3): 555–556
ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2014.949262

informa
healthcare

COMMENTARY

Sirolimus plus calcineurin inhibitors and methotrexate: is more necessarily better?

Basem M. William & Marcos de Lima

Stem Cell Transplantation Program, Department of Medicine, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH, USA

Graft-versus-host disease (GVHD) prophylaxis using calcineurin inhibitors was introduced in allogeneic stem cell transplant (alloSCT) in the 1980s. Early work of Storb, Deeg and Ringden established the pivotal role of cyclosporine A, which was shown to be more effective as a single agent than methotrexate [1]. It was also shown that combination of cyclosporine A with methotrexate is synergistic, and hence established the combination as the standard of care for GVHD prevention [2]. However, acute and chronic GVHD rates remain stubbornly substantial, and GVHD is one of the major causes of treatment failure in alloSCT. Multiple strategies have been tested in randomized and non-randomized trials, including T-cell depletion, cytokine blockade and reducing triggers of inflammation, to name a few. Most approaches failed to demonstrate a clear survival benefit, albeit lower rates of GVHD. Although many of these studies were not sufficiently powered to detect small changes in overall survival, they often reflected the fact that decreasing GVHD rates were "compensated" by higher rates of malignancy relapse or opportunistic infections.

The classic conundrum of alloSCT is that GVH and graft-versus-leukemia/lymphoma (GVL) effects are often inseparable. This classic dogma has been challenged by recent work delineating the role of regulatory T-cells (Tregs) as modulators of GVHD. Sirolimus (rapamycin) is a naturally occurring macrolide with antiviral, antifungal, antineoplastic and immunosuppressive properties. Sirolimus binds to FKBP-12 to form an immunosuppressive complex that inhibits the mammalian target of rapamycin (mTOR), resulting in decreased T-cell proliferation and activation. Sirolimus has been shown to induce preferential Tregs expansion *in vitro* and *in vivo* [3], and it has been used in solid organ transplant, in the treatment of acute and chronic GVHD, and also in combination with other agents as a "calcineurin-free" GVHD prevention regimen after alloSCT. Interestingly, mTOR inhibitors have clinical activity in patients with relapsed and refractory lymphoma with both indolent and aggressive histologies [4]. Therefore, sirolimus offers two theoretical advantages as a GVHD prevention agent after alloSCT for lymphomas: (1) it would induce selective Tregs expansion and hence attenuation of GVHD, and (2) it would control lymphoma as a "maintenance" agent and potentially would decrease the incidence of post-transplant relapse. The drug is not devoid of side effects, including thrombotic microangiopathy, which seems to complicate myeloablative transplants more often than that in does IN transplants using reduced-intensity preparative regimens [5]. A retrospective analysis by Armand *et al*. showed that sirolimus decreased the incidence of lymphoma progression after alloSCT [6]. Conversely, the randomized comparison of tacrolimus and sirolimus versus tacrolimus and methotrexate for GVHD prophylaxis (limited to human leukocyte antigen [HLA]-matched, related donor alloSCT) performed by the Blood and Marrow Transplant Clinical Trials Network failed to show a survival or GVHD advantage for the tacrolimus/sirolimus combination.

Ceberio's study in this issue of ***Leukemia and Lymphoma*** [7] would suggest that sirolimus has delivered partially on its promise. The authors showed a low incidence of acute and chronic GVHD which translated into favorable progression-free and overall survival, but disease progression remained the leading cause of treatment failure. Relapse rates were actually similar to those reported by others [8]. Interestingly, cytomegalovirus (CMV) reactivation rates were low, suggesting a direct antiviral effect of sirolimus.

Taken in aggregate, patient heterogeneity complicates the interpretation of the available studies. Examples include the use of different conditioning regimens, dissimilar histologic types of lymphomas, disease status at transplant, chemosensitivity, inconsistent use of positron emission tomography (PET) to document disease status before transplant, use of T-cell depleting agents and use of peritransplant rituximab, which all conspire to limit our ability to draw proper conclusions in the setting of non-Hodgkin lymphoma.

Correspondence: Basem M. William, MD, MRCP (UK), Stem Cell Transplantation Program, Department of Medicine, University Hospitals Seidman Cancer Center, Case Western Reserve University, 11100 Euclid Ave, LKS 5079, Cleveland, OH 44106, USA. Tel: 216-983-3276. Fax: 216-201-5451. E-mail basem.william@uhhospitals.org

This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

Therefore, it is possible that certain patient subsets would benefit from the addition, or substitution, of sirolimus in a GVHD prophylaxis regimen. However, that subset remains to be defined.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

References

[1] Storb R, Deeg HJ, Thomas ED, et al. Marrow transplantation for chronic myelocytic leukemia: a controlled trial of cyclosporine versus methotrexate for prophylaxis of graft-versus-host disease. Blood 1985; 66:698–702.

[2] Chao NJ, Schmidt GM, Niland JC, et al. Cyclosporine, methotrexate, and prednisone compared with cyclosporine and prednisone for prophylaxis of acute graft-versus-host disease. N Engl J Med 1993; 329:1225–1230.

[3] Zeiser R, Leveson-Gower DB, Zambricki EA, et al. Differential impact of mammalian target of rapamycin inhibition on CD4 + CD25 + Foxp3 + regulatory T cells compared with conventional CD4 + T cells. Blood 2008;111:453–462.

[4] Witzig TE, Reeder CB, LaPlant BR, et al. A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma. Leukemia 2011;25:341–347.

[5] Cutler C, Logan BR, Nakamura R, et al. Tacrolimus/sirolimus vs. tacrolimus/methotrexate for graft-vs.-host disease prophylaxis after HLA-matched, related donor hematopoietic stem cell transplantation: results of Blood and Marrow Transplant Clinical Trials Network Trial 0402. Blood 2012;120(Suppl. 1): Abstract 739.

[6] Armand P, Gannamaneni S, Kim HT, et al. Improved survival in lymphoma patients receiving sirolimus for graft-versus-host disease prophylaxis after allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning. J Clin Oncol 2008;26:5767–5774.

[7] Ceberio I, Devlin SM, Sauter C, et al. Sirolimus, tacrolimus and low-dose methotrexate based graft-versus-host disease prophylaxis after non-ablative or reduced intensity conditioning in related and unrelated donor allogeneic hematopoietic cell transplant. Leuk Lymphoma 2015;56:663–670.

[8] McClune BL, Ahn KW, Wang HL, et al. Allotransplantation for patients age >/ = 40 years with non-hodgkin lymphoma: encouraging progression-free survival. Biol Blood Marrow Transplant 2014;20: 960–968.