Rabbit Antithymocyte Globulin Versus Alemtuzumab in Allogeneic Stem Cell Transplantation: A Meta-Analysis

Hongju Yan, Lei Gao, Xi Zhang

Abstract—Rabbit antithymocyte globulin (ATG) and alemtuzumab have been used for graft-versus-host disease (GVHD) prophylaxis in allogeneic haematopoietic stem cell transplantation (allo-HSCT), but which is more efficient remain unclear. We perform a meta-analysis of all studies comparing rabbit ATG and alemtuzumab in GVHD prophylaxis in allogeneic haematopoietic stem cell transplantation (HSCT) to evaluate their benefits and drawbacks. There are 7 studies (one prospective and six retrospective) for comparing rabbit ATG vs alemtuzumab in GVHD prophylaxis with 622 patients. Our results showed that the incidence of grade II-IV acute GVHD (aGVHD) (RR 1.51, 95% CI 0.97–2.34, P = 0.07), incidence of grade III-IV acute GVHD (aGVHD (RR 1.48, 95% CI 0.63–3.47, P = 0.37) had a statistically non-significant reduction in alemtuzumab group, however, alemtuzumab significantly impaired OS (HR 0.61 (95% CI 0.41–0.90, P = 0.01) compared with ATG. The incidence of overall chronic GVHD (RR 0.97, 95% CI 0.67–1.40, P = 0.87) and the incidence of relapse (RR 1.03, 95% CI 0.72–1.47, P = 0.88) were similar in the two groups. We propose that using alemtuzumab for GVHD prophylaxis is effective for allogeneic stem cell transplantation due to the efficacy in grade III/IV acute GVHD, but OS is impaired compared with ATG group.

Index Terms—Haematopoietic Stem Cell Transplantation, ATG, Alemtuzumab, GVHD, Meta-Analysis.

I. INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for patients with haematological malignancies, bone marrow failure syndrome, and some inherited metabolic disorders. However, GVHD is still a major cause of morbidity and mortality [1]–[2]. Serotherapy, which consists of antithymocyte globulin (ATG), a polyclonal antibody, or the monoclonal antibody alemtuzumab, is normally used for GVHD prophylaxis. ATG is a polyclonal immunoglobulin preparation obtained by immunization of rabbits or horses with human thymocytes or T cell lines. Alemtuzumab is a humanized monoclonal antibody specific for CD52. In the HSCT setting, both types of serotherapy are used to eliminate T cells, but they also present additional drawbacks. There are 7 studies (one prospective and six retrospective) for comparing rabbit ATG vs alemtuzumab in GVHD prophylaxis with 622 patients. Our results showed that the incidence of grade II-IV acute GVHD (aGVHD) (RR 1.51, 95% CI 0.97–2.34, P = 0.07), incidence of grade III-IV acute GVHD (aGVHD (RR 1.48, 95% CI 0.63–3.47, P = 0.37) had a statistically non-significant reduction in alemtuzumab group, however, alemtuzumab significantly impaired OS (HR 0.61 (95% CI 0.41–0.90, P = 0.01) compared with ATG. The incidence of overall chronic GVHD (RR 0.97, 95% CI 0.67–1.40, P = 0.87) and the incidence of relapse (RR 1.03, 95% CI 0.72–1.47, P = 0.88) were similar in the two groups. We propose that using alemtuzumab for GVHD prophylaxis is effective for allogeneic stem cell transplantation due to the efficacy in grade III/IV acute GVHD, but OS is impaired compared with ATG group.

II. METHODS

A. Inclusion criteria

The inclusion criteria consisted of (i) participants without the restrictions of special, irrespective of age, disease, graft source and donor; (ii) studies that compared the prophylactic use of rabbit ATG and alemtuzumab in patients; (iii) allo-HSCT for haematological diseases (irrespective of disease stage); (iv) use antithymocyte or alemtuzumab in any dose or given duration; (v) studies that reported data and included details regarding demographic, transplant, treatment, and outcome variables.

B. Literature search

Two authors independently conducted an electronic literature search in Pubmed, EMBASE and MEDLINE, we used a broad search strategy to identify both prospective and retrospective clinical studies evaluating the outcome of prophylactic rabbit ATG and alemtuzumab use in allo-HSCT from January 2000 to March 2015. Studies earlier than 2000 were not included because considerable progress in supportive care and antibody manufacturing has been made during the recent 10 years. The search was conducted in March 2015. We performed manual selection by reading the abstracts, and further selection by reading full texts. The experts in the field and the authors of published studies were not contacted. To reduce potential language bias, language restriction was not applied.

Hongju Yan, Department of Haematology, Xinqiao Hospital, The Third Military Medical University, Xinqiao Street, Chongqing, China.

Lei Gao, Department of Haematology, Xinqiao Hospital, The Third Military Medical University, Xinqiao Street, Chongqing, China.

Xi Zhang, Department of Haematology, Xinqiao Hospital, The Third Military Medical University, Xinqiao Street, Chongqing, China.
C. Outcomes

The outcomes were extracted regarding the benefits and drawbacks associated with the treatments. Their included (1) OS; (2) GVHD incidence; and (3) relapse.

D. Study selection, quality assessment, and data extraction

Two reviewers independently read the titles and abstracts of all studies identified through the literature search to determine whether they met the predefined inclusion criteria. The same set of reviewers extracted data regarding the benefits (OS, GVHD incidence and relapse) associated with the compared treatments using a standardized data extraction form, according to the guidelines proposed by The Cochrane Collaboration. The full search strategy and data selection are described in Fig.1. The quality of the study was evaluated using ratings on the Newcastle-Ottawa Scale [17].

Fig.1. Flow Diagram Showing the Process of Identifying and Selecting Relevant Studies

E. Data analysis and statistical methods

Time-to-event data (OS) was pooled and was reported as hazard ratios (HR), meanwhile, dichotomous data (incidence of GVHD, relapse were pooled and are reported as risk ratios (RR)[18], with 95% confidence intervals (CI) under a random effects model, respectively[19]. We extracted these data according to the method described by Tierney et al[20] if time-to-event were unavailable for direct extraction. This method needs calculation of the hazard ratio from different parameters using indirect calculation of the variance and the number of observed events minus the number of expected events. A formal statistical test for heterogeneity using the chi-square [19] and I² [21] tests was conducted (I² >30%, moderate heterogeneity; I² >75%, severe heterogeneity).

This meta-analysis was performed using Review Manager Software (Review Manager, Version 5.3, The Cochrane Collaboration 2014, Copenhagen).

III. RESULTS

Table 1: Characteristics of the studies included into the meta-analysis

Seven studies that enrolled a total of 622 patients from 2005 to 2015 were included in this meta-analysis. Table 1 summarizes the details related to patient characteristics. The assessment of study quality is shown in table 2.

A. Overall survival (OS)

Kaplan–Meier plots of overall survival were available in 6 out of the 7 studies. A total of 553 patients were analysed, and the pooled HR showed a statistically significant benefit for OS with the use of rabbit ATG for the prevention of GVHD (fig.2.). The pooled hazard ratio for the comparison of rabbit ATG versus alemtuzumab was 0.61 (95% CI 0.41–0.90, P = 0.01). The heterogeneity was low among the studies (I² =0%).
Regarding the incidence of grade II-IV acute GVHD (aGVHD) (Fig.3.a), 398 patients from 4 studies showed a statistically non-significant reduction in the alemtuzumab arm (RR 1.51, 95% CI 0.97–2.34, P = 0.07). The heterogeneity was low among the studies (I² = 0%). Regarding the incidence of grade III-IV aGVHD (Fig.3.b), 435 patients from 5 studies showed a statistically non-significant reduction in the alemtuzumab arm (RR 1.48, 95% CI 0.63–3.47, P = 0.37). The heterogeneity was low among the studies (I² = 0%). Regarding the incidence of overall chronic GVHD (Fig.3.c), 514 patients from 5 studies showed a statistically non-significant effect with rabbit ATG versus alemtuzumab (RR 0.97, 95% CI 0.67–1.40, P = 0.87). The heterogeneity was low among the studies (I² = 26%).

Regarding the incidence of relapse (Fig.4.), 359 patients from 4 studies showed a statistically non-significant effect with rabbit ATG versus alemtuzumab (RR 1.03, 95% CI 0.72–1.47, P = 0.88). The statistically non-significant heterogeneity was low among the studies (I² = 30%).

**Table 2: Assessment of Study Quality**

<table>
<thead>
<tr>
<th>AuthorYear</th>
<th>Quality Indicators From Newcastle-Ottawa Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Julisson2006</td>
<td>No, Yes, No, Yes, Yes, Yes, Yes, No</td>
</tr>
<tr>
<td>Kopev2005</td>
<td>No, Yes, Yes, Yes, Yes, Yes, No, No</td>
</tr>
<tr>
<td>Nord2011</td>
<td>No, Yes, Yes, Yes, Yes, Yes, Yes, No</td>
</tr>
<tr>
<td>Park2008</td>
<td>No, Yes, Yes, Yes, Yes, Yes, Yes, No</td>
</tr>
<tr>
<td>Nord2011</td>
<td>No, Yes, Yes, Yes, Yes, Yes, Yes, No</td>
</tr>
<tr>
<td>Park2008</td>
<td>No, Yes, Yes, Yes, Yes, Yes, Yes, No</td>
</tr>
<tr>
<td>Julisson2006</td>
<td>No, Yes, Yes, Yes, Yes, Yes, Yes, No</td>
</tr>
<tr>
<td>Kopev2005</td>
<td>No, Yes, Yes, Yes, Yes, Yes, Yes, No</td>
</tr>
<tr>
<td>Nord2011</td>
<td>No, Yes, Yes, Yes, Yes, Yes, Yes, No</td>
</tr>
<tr>
<td>Park2008</td>
<td>No, Yes, Yes, Yes, Yes, Yes, Yes, No</td>
</tr>
</tbody>
</table>

*For case-control studies, indicates cases independently validated; consecutive or obviously representative cases of cases 3. community controls 4, disease controls 5, study controls for additional factor(s) 6. Ascertainment of exposure by secure record; same method of ascertainment used for cases and controls 8. Non-response rate same for the same cases and controls 9. For cohort studies, indicates exposed cohort truly representative, non-exposed cohort drawn from the same community 10. Ascertainment of exposure, outcome of interest not present at start 11. Cohorts comparable on basis of age, sex, and other factor(s) 12. Quality of outcome assessment 7. Follow-up long enough for outcomes to occur 8. Complete accounting for cohort.
IV. DISCUSSION

GVHD remains a serious clinical complication for patients undergoing allo-HSCT for haematological diseases. This systematic review and meta-analysis is the first to evaluate the efficacy of rabbit ATG versus alemtuzumab in GVHD prophylaxis before infusion of stem cells. Seven studies met the inclusion criteria. The pretreatment, basic diseases, stem cell source, donor type, age, follow-up times, doses of rabbit ATG, and dose of alemtuzumab were different between studies, but the rabbit ATG and alemtuzumab groups in each study were roughly consistent in several aspects. The baselines were comparable, therefore, the results are relatively reliable.

Our outcomes showed no obvious advantage of alemtuzumab in reducing grade III-IV aGVHD and grade II-IV aGVHD, and OS has not been improved in alemtuzumab group, these outcomes might be related to slow immune reconstitution and high mixed donor chimerism in alemtuzumab group, so fungal infections and fatal bacterial infections were more frequent, OS was impaired. We just chose rabbit ATG and did not horse ATG or mixed ATG to reduce heterogeneity, and use the incidence of initial aGVHD for statistical analysis because we thoughted aGVHD after donor lymphocyte infusion (DLI) was induced by treating residual disease and/or mixed chimerism and when the antibody has lose efficacy in human body in either sero-therapies. Busemann et al.[23] studied alemtuzumab compared with the rabbit ATG/no AB, and used rabbit ATG in unrelated or mismatched transplantation but no antibody in HLA-identical sibling transplantation, so we only could extract OS between unrelated donor in two sero-therapies and Juliusson et al.[26] analyzed rabbit ATG, alemtuzumab-30mg and alemtuzumab-90mg, we could not extract OS between rabbit ATG and alemtuzumab, in this study, OS was excellent in the rabbit ATG-treated group, and the same in alemtuzumab-30mg, but impaired in the alemtuzumab-90mg group.

In conclusion, our results demonstrate that, whereas alemtuzumab may be effective in preventing grade III-IV aGVHD and grade II-IV aGVHD. The incidence of overall chronic GVHD and the incidence of relapse were similar in two group. However, OS has been impaired in alemtuzumab. Our meta-analysis is mainly based on retrospective studies with a lack of internal validity, and the sample size is relatively small. Therefore, the conclusions should be interpreted with caution; more sufficient evidence is needed from future prospective randomized trials based on the type of transplant, dose of antibody, pretreatment, age of patient and disease types. Nevertheless, we propose that using alemtuzumab for GVHD prophylaxis is effective for allo-HSCT due to the efficacy in grade III/IV aGVHD and grade II-IV aGVHD, but OS is impaired compared with rabbit ATG group, how to speed up immune reconstitution, increase full donor chimerism rate and decrease infection rate still need great efforts.

CONFLICTS OF INTEREST

Authors declare that they have no conflicts of interests.

ACKNOWLEDGMENT

We thank the librarians of The Third Military Medical University for providing statistical books. We give our thanks to Mr. Zhang for all his kindness and help.

REFERENCES


80  www.ijntr.org

Hongju Yan, she is a postgraduate student of The Third Military Medical University, Chongqing, China. Her research interests in hematopoietic stem cell transplantation.
Lei Gao, she is a professor with a Ph.D in Xinqiao Hospital, The Third Military Medical University, Chongqing, China. Her research interests in hematopoietic stem cell transplantation for treating leukemia, aplastic, lymphoma.
Xi Zhang, he is a professor with a Ph.D in Xinqiao Hospital, The Third Military Medical University, His research interests in hematopoietic stem cell transplantation, the treatment of refractory autoimmune diseases of blood, individualized treatment of leukemia, lymphoma.