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Mycophenolate mofetil vs. methotrexate for the prevention of graft-versus-host-disease – Systematic review and meta-analysis

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ABSTRACT

We performed a systematic review and meta-analysis of all trials comparing MMF and methotrexate as GVHD prophylaxis. Our search yielded 11 studies; 3 were randomized-control trials (RCTs). While the incidence of grades 2–4 acute GVHD was comparable, the incidence of grades 3 and 4 acute GVHD was higher in patients given MMF (RR 1.61; 95% CI 1.18–2.30). Incidence of mucositis was lower (RR 0.35; 95% CI 0.25–0.49) and time to engraftment was shorter (mean difference (−3.6); 95% CI −5.5 to −1.7) in patients given MMF. All other analyzed transplantation outcomes were comparable. We conclude that MMF, compared to methotrexate, is associated with increased severity of acute GVHD. Robustness of these results is hampered by the small number of RCTs.

1. Introduction

Graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation (HCT) is associated with significant morbidity and mortality [1,2]. Despite prophylactic measures, the incidence of acute GVHD is estimated to be 40–75% [3]. The tight association between the degree of GVHD and the non-relapse mortality resulted in vigorous attempts to find strategies to decrease its severity [4].

Several approaches have been studied and are currently used as part of transplantation protocols. Currently, in most centers GVHD prophylaxis is largely based on a calcineurin inhibitor, such as cyclosporine or tacrolimus, and a short course of methotrexate [5]. We have previously shown that the combination of a calcineurin inhibitor (CNI) with methotrexate is superior to monotherapy [6]. Other pharmacologic options include corticosteroids, mycophenolate mofetil (MMF) and sirolimus in various combinations [5].

There are several caveats with the administration of methotrexate, mainly the inhibition of hematopoietic engraftment, worsening of oral mucositis and less frequently, pulmonary and renal toxicity. MMF, usually not associated with these complications, might potentially substitute methotrexate for GVHD prophylaxis.

Thus, we aimed to systematically review the literature for all comparative trials, comparing methotrexate to MMF as prophylaxis for GVHD.

2. Methods

2.1. Data sources

We conducted a comprehensive search strategy to identify both published and unpublished studies, with no restriction on language or study years. We included all comparative studies, both randomized controlled trials (RCTs) and non-randomized studies, in patients given allografts for hematologic malignancies and GVHD prophylaxis with either MMF or methotrexate (both in combination with a calcineurin inhibitor). We included studies that included different types of donors (related and unrelated) and different graft sources (G-mobilized peripheral blood hematopoietic cells and bone marrow). Relevant trials were identified by searching The Cochrane Library (current) and PubMed (January 1966 and onwards). We searched the following conference proceedings (2002–2011): the American Society of Hematology, the American Society of Clinical Oncology, and the European Hematology Association, the IBMTR (International Bone Marrow Transplant Registry) and EBMT (European group for Blood and Marrow Transplantation) for relevant abstracts. The corresponding author of each included trial was contacted for information regarding unpublished trials or complementary information on their own trial.

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We used National Library of Medicine, Medical Subject Headings (MeSH), terminology and the following search term for all electronic databases: (mycophenolate OR mycophenolic OR MMF) AND (methotrexate OR MTX) AND allogeneic [MeSH] and crossed with the search sentence: prospective OR longitudinal OR cohort OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] NOT (animals [mh] NOT human [mh]).

2.2. Study selection

One review author (RR) inspected the title and the abstract of each reference identified in the search and applied the inclusion criteria. Where relevant articles were identified, the full article was obtained and inspected independently by two review authors and inclusion criteria were applied (RR and AG). Table 1 provides the characteristics of the included studies.

2.3. Outcomes

Primary outcomes were acute GVHD and all cause mortality. For the GVHD outcome, we chose to evaluate cumulative incidence at day 100 post HCT, based on the classical definition of GVHD.

Secondary outcomes included extensive chronic GVHD, relapse rate, and non relapse mortality. When long term follow-up was reported, mortality data at the longest available time point was used [6,7]. We also evaluated the rate of mucositis and the time to engraftment of both neutrophils and platelets. These outcomes were evaluated according to the study definition, as there were numerous classifications and definitions. Disease risk for relapse was evaluated according to previously published criteria [8].

2.4. Risk of bias assessment

Trials fulfilling inclusion criteria were assessed for methodological quality by the two reviewers. We performed sensitivity analyses based on the risk of bias items listed below. For all items, no reporting of data in the studies was considered as a high risk for bias. In the final sensitivity analysis we separately analyzed the RCTs and the non-randomized trials.

In all studies we extracted information regarding intention to treat analysis, sample size, reporting of exclusions after randomization and their cause – a study with a dropout rate higher than 10% was considered at a high risk of bias/potentially biased, and reporting the number and causes of deaths.

For randomized trials, we used the Cochrane Collaboration's tool for assessing risk of bias. Table 2 provides a description of what was reported in the study and a subjective judgment regarding protection from bias: low risk, high risk of bias or unclear risk (Cochrane handbook version 5.1.0.; available from www.cochrane-handbook.org).

For prospective non-randomized studies we used the Newcastle-Ottawa scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) to assess whether the study adjusted for the confounders listed in Table 2. For each study, we summed up the number of the well-comparable parameters to a numeric Ottawa score, which was used to grade the quality of the study.

For all study designs we assessed the comparability of the study groups based on these confounders: age, status of disease (complete remission vs. persistent disease), and intensity of conditioning (myeloablative vs. reduced intensity).

2.5. Data synthesis

Dichotomous data were analyzed by calculating the relative risk (RR) for each trial with its 95% confidence intervals (CI). We used the Mantel-Haenszel methods to analyze dichotomous outcome [9]. We analyzed continuous data by calculating weighted mean difference (WMD) using the mean and standard deviation of each trial and calculating the effect size (average mean difference) and the 95% CI, whenever comparisons made between the mean duration of symptoms in the two groups were normally distributed. The mean difference estimates the amount by which the experimental intervention changes the outcome on average compared with the control. We used mean difference as a summary statistic when outcome measurements in all studies were calculated on the same scale [9].

2.6. Heterogeneity and publication bias

Heterogeneity in the results of the trials was assessed by calculating a test of heterogeneity (Chi-square and I^2). I^2 expresses the heterogeneity after adjustment to the degree of freedom (the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error) [9]. We anticipated between-trial variation in estimation of morbidity and mortality for trials comparing patients at different risk levels, given different allografts, and using different prophylaxis regimens. Subgroup analyses were performed in order to assess the impact of these possible sources of heterogeneity on the main results. A random effects model was used in cases of significant heterogeneity ($I^2 > 50\%$).

In addition, we conducted meta-regression on the log risk ratio of grades 3 and 4 GVHD, assessing the effect of the per protocol MMF daily dose in each study on effect estimates for the primary outcome. All analyses were performed with Review Manger (RevMan) 5.

3. Results

The search yielded 111 potentially relevant trials of which 17 [10–26] were considered for further investigation. Of these, 10 studies were excluded [17–26] (Fig. 1). In addition, 5 abstract proceedings were identified and also included in the analysis [27–31]. One of the abstract proceedings [29] was simultaneously published as a journal paper [11]. Eleven trials, enrolling 1076 patients conducted between the years 1999 and 2010 fulfilled inclusion criteria [10–16,27,28,30,31]. Three trials were randomized controlled trials [11,12,15]. Two trials were prospective one arm interventional trials with comparison to historical controls [10,28]. All other 6 trials were retrospective comparative analyses [13,14,16,27,30,31]. One of the randomized controlled trials was an interim analysis report and the authors reported on data of 39 out of 45 patients originally recruited to the study [11]. The same study was also published as a conference proceeding abstract [29], however only data published in the original article were incorporated to the meta-analysis. Two authors responded to our request for additional data [10,30]. These data were incorporated to the meta-analysis.

All trials included patients undergoing transplantation from a matched related or unrelated donor following either myeloablative or reduced intensity conditioning (RIC) and all used T cell-repleted allografts. In 1 study, a small proportion of the patients were given anti-thymocyte globulin [15] Data regarding demographics, host and donor characteristics, and transplantation protocol are summarized in Table 1. The MMF-based regimen administered was heterogeneous, both in the total daily dose (ranging from 1.5 to 3 g) and in the duration of administration (ranging from 2 weeks to 6 months). The comparative methotrexate-based regimen also varied among the different trials, although most used a single dose of 15 mg/m^2 and 2–3 additional doses of 10 mg/m^2. All studies assessed grading of acute GVHD according to the classical