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Individualised doses of anti-thymocyte globulin and immune recovery after allogeneic HSCT

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Transplanted mature donor T cells play a pivotal role after allogeneic haematopoietic stem-cell transplantation (HSCT). T cells protect patients from viral infections and mediate graft-versus-tumour effects.[1] However, T-cell responses can lead to the development of graft-versus-host disease (GVHD). Rabbit anti-thymocyte globulins are polyclonal immunoglobulins obtained from hyperimmune sera of rabbits immunised with human thymocytes (ATG-T) or the human Jurkat T-cell line (ATLG).[2] Anti-thymocyte globulin has a half-life of 5–14 days,[3] and thus remains present at substantial concentrations at transplantation when given during the conditioning regimen. Consequently, anti-thymocyte globulin has been largely used with the aim of preventing graft rejection through depletion of host T cells and preventing GVHD through partial depletion of donor T cells.[2] Three phase 3 trials have assessed the effect of pre-transplantation ATG-T (4·5 mg/kg total dose)[4] or ATLG (60 mg/kg total dose)[5,6] administration in addition to standard GVHD prophylaxis in patients undergoing allogeneic HSCT from unrelated donors. Although the three trials showed lower GVHD incidence in patients randomly assigned to the anti-thymocyte globulin group, patients who received anti-thymocyte globulin had similar overall survival to control patients in the study by Finke and colleagues,[5] higher overall survival than control patients in the study by Walker and colleagues,[4] and lower overall survival compared with control patients in the study by Soiffer and colleagues.[6]

How to explain these divergent results? Over the past decade, Rick Admiraal and colleagues have pioneered pharmacokinetic analyses of anti-thymocyte globulin in allogeneic HSCT recipients and showed that administration of a fixed weight-based dose of anti-thymocyte globulin led to unpredictable and highly variable anti-thymocyte globulin exposure.[3] Indeed, there were non-linear relationships between ATG-T clearance and bodyweight and between ATG-T clearance and absolute lymphocyte counts at ATG-T initiation.[7] Consequently, pre-transplantation and post-transplantation anti-thymocyte globulin exposures could be calculated by a pharmacodynamic model including recipient bodyweight and absolute lymphocyte count at anti-thymocyte globulin initiation. In a cohort of adult patients with acute leukaemia receiving allogeneic peripheral blood stem cells and a fixed dose of ATG-T (8 mg/kg total dose started on day 8 before transplantation), Admiraal and colleagues[8] showed that

post-transplantation anti-thymocyte globulin exposure below the optimum increased the incidence of grade 3–4 acute GVHD and non-relapse mortality and decreased overall survival.[8] Furthermore, post-transplantation anti-thymocyte globulin exposure above the optimum increased relapse incidence (due to lower graft-versus-tumour effects) and decreased overall survival.

In *The Lancet Haematology*, Rick Admiraal and colleagues[9] report the results of a prospective single arm phase 2 study of individualised dosing of ATG-T for paediatric unrelated allogeneic HSCT.[9] The study is based on a previous study by the authors, which showed that successful $CD4^+$ immune reconstitution (defined as $CD4^+$ T cells $>0{\cdot}05\times10^9$ per L in two consecutive measurements within 100 days after transplantation) was less frequent in patients with post-transplantation anti-thymocyte globulin area under the curve (AUC) above the first quartile in the subgroup of cord blood transplantation recipients, and in those with post-transplantation anti-thymocyte globulin AUC above the third quartile in the subgroup of bone marrow or peripheral blood stem cell recipients.[3] Furthermore, successful immune reconstitution correlated with lower non-relapse mortality and better overall survival. The primary endpoint of the trial was the incidence of immune reconstitution. The authors hypothesised that individualising anti-thymocyte globulin doses would increase immune reconstitution from 62% in an historical cohort of 100 patients given ATG-T at 10 mg/kg fixed total dose (starting 5 days before transplantation) to 80% in the trial patients. ATG-T dosing individualisation was based on bodyweight, absolute lymphocyte count at anti-thymocyte globulin initiation, and stem-cell source (lower post-transplantation anti-thymocyte globulin dose for cord blood transplantation recipients compared with bone marrow or peripheral blood stem cell recipients) and ranged from 2–10 mg/kg total dose. ATG-T was started 9 days before transplantation. The main observation was that immune reconstitution was seen in 41 (80%) of 51 evaluable patients, meeting the study primary endpoint. Regarding secondary endpoints, incidences of graft failure, relapse, and grade 3–4 acute GVHD were similar in the trial and historical patients, whereas the trial patients had a lower incidence of Epstein-Barr virus (3·5% [95% CI 0·6–10·7]) than did historical patients (20% [13–28]; HR 0·17, 95% CI 0·04–0·77; p=0·022). 3-year overall survival was 81% (95% CI 71–92) in trial patients versus 66% (57–76) in control patients (p=0·11). In post-hoc analyses including trial and control patients, successful immune reconstitution was associated with lower non-relapse mortality and improved overall survival.

This study by Admiraal and colleagues is remarkable since it is, to my knowledge, the first prospective study investigating individualised dosing of anti-thymocyte globulin in allogeneic HSCT. Although the primary endpoint of the study was met, one could argue that a phase 3 design with overall survival as the primary endpoint would have provided more definitive evidence of the importance of individualising anti-thymocyte globulin dosing in allogeneic HSCT recipients. The investigators elected not to select this design because of their retrospective data showing that fixed bodyweight-based dosing would have led to anti-thymocyte globulin overexposure in many patients with low absolute lymphocyte count or high bodyweight (and particularly among cord blood transplant recipients). A post-hoc analysis of trial and historical patients combined revealed that successful immune reconstitution predicted better overall survival, supporting the role of immune reconstitution as a surrogate marker for overall survival. A possible limitation of the study is that all stem-cell sources were allowed. However, a subgroup analysis showed that immune reconstitution was reached in a similar proportion of bone marrow transplantation (77% [95% CI 54–89]) and cord blood transplantation (87% [61–96]) recipients.

Where do we go from here? There is accumulating evidence that post-transplantation cyclophosphamide might be an alternative to anti-thymocyte globulin as GVHD prophylaxis in unrelated allogeneic bone marrow or peripheral blood stem-cell recipients.[10] The study by Admiraal and colleagues could serve as the basis for a phase 3 trial to compare individualised doses of anti-thymocyte globulin with post-transplantation cyclophosphamide in patients given bone marrow or peripheral blood stem cells from unrelated donors.

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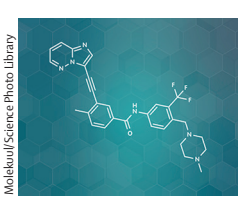
Matchpoint: the game is not over for blast-phase chronic myeloid leukaemia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In the era of tyrosine-kinase inhibitors (TKIs), chronic myeloid leukaemia is no longer a deadly disease. However, a small proportion of patients still have a short life expectancy. The SPIRIT study[1] showed a 15-year relative survival of 96% (95% CI 92–99) in patients with chronic myeloid leukaemia, and the CML IV study[2] showed a 10-year relative survival of 92% (95% CI 89–95). Chronic myeloid leukaemia progression was recorded in 45 (5·7%) of 789 patients recruited in the SPIRIT trial, including 35 (4·4%) with blast phase.[1] 25 (55%) of the 45 patients in accelerated phase or blast crisis died. Median survival after progression was 7·9 months in the CML IV trial.[2] Conversely, little is known about the epidemiology of the patients who are newly diagnosed in blast phase.

Patients in lymphoid blast phase are usually treated according to protocols designed for Philadelphia-positive acute lymphocytic leukaemia. A trend for improved survival with more potent TKIs has been observed with the hyper-CVAD regimen. In a study of ponatinib (45 mg daily for 14 days during cycle 1 and then continuously),[3] two fatal myocardial events were recorded. No further vascular events occurred after ponatinib dose reduction to 30 mg daily after cycle 1 and 15 mg daily after complete molecular response.[3] Patients with myeloid blast phase are similarly treated with chemotherapy and TKIs. The 2020 European LeukemiaNet guidelines recommend the use of dasatinib or ponatinib in combination with acute myeloid leukaemia regimens such as fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (FLAG-IDA) followed by prompt allogeneic haematopoietic stem-cell transplantation (HSCT) if possible.[4]

In *The Lancet Haematology*, Mhairi Copland and colleagues[5] report the results of the first phase 1/2, dose-finding trial of ponatinib in combination with the FLAG-IDA regimen for patients with blast-phase chronic myeloid leukaemia (MATCHPOINT). Using a Bayesian model considering both activity and tolerability (the EffTox model), Copland and colleagues found that ponatinib 30 mg daily with FLAG-IDA reached the prespecified thresholds for activity and toxicity, with a 68% estimated probability of activity (95% credible interval 47–84; 45% or more required in the model) and a 25% probability of toxicity (8–41; 40% or less