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Background: Fludarabine is a common constituent of conditioning for hematopoietic cell transplantation (HCT). It is a prodrug that is dephosphorylated in plasma to its measurable metabolite, F-ara-A, which after intracellular rephosphorylation interferes with DNA replication, transcription and translation, and induces apoptosis.

Due to variable renal clearance, F-ara-A levels on day 0 are variable. The clinical relevance of the F-ara-A persisting in plasma is unknown. The goal of this study was to assess the relationship between F-ara-A levels on day 0 and clinical outcomes including GVHD, infections, relapse and death.

Patients and Methods: We included 166 consecutive patients undergoing first allogeneic transplantation of filgrastim-mobilized blood stem cells for a hematologic malignancy between December 2008 and 2012. Conditioning was myeloablative, and included fludarabine (50 mg/m^2 daily from days -6 to -2), busulfan and antithymocyte globulin. Additional GVHD prophylaxis included methotrexate and cyclosporine. The interval between the last fludarabine dose and graft infusion was 48-72 hours. F-ara-A serum levels were measured using mass spectrometry.

Results: In univariate analyses, there was no difference in median F-ara-A levels between patients who did *vs* did not develop acute GVHD grade 2-4, acute GVHD grade 3-4, any chronic GVHD, chronic GVHD needing systemic therapy (NST), CMV reactivation above our threshold for preemptive therapy (25,000 IU/mL), post-transplant lymphoproliferative disorder (PTLD), relapse, death or non-relapse death (Figure 1).

In multivariate analyses, there was no difference in the likelihood of developing any one of the outcomes between patients whose F-ara-A level was above *vs* below median (14 ng/mL). We also assessed for differences in the likelihood of developing each outcome between patients with levels in the fourth quartile (21-104 ng/mL) *vs* the first quartile (1-9 ng/mL). Again, in this analysis, there was no difference for any outcome.

We also noted a weak correlation between F-ara-A levels on day 0 and the day of neutrophil engraftment ($r=0.16$, $p=0.04$), and a trend towards more bacterial infections in patients with F-ara-A levels in the fourth *vs* first quartile.

Discussion: The results suggest that there is no or minimal impact of day 0 F-ara-A levels on clinical outcomes. This may be due to the fact that F-ara-A levels on day 0 were relatively low (1-104 ng/mL, median 14 ng/mL) compared to levels 1-4 hours after fludarabine infusion ($\sim$1,000 ng/mL).

Conclusion: Day 0 F-ara-A levels are highly variable (1-104 ng/mL), likely due to variable renal function. Given that we found no association between the day 0 levels and clinical outcomes we do not support delaying graft infusion until F-ara-A level has dropped below a certain level, as long as the last fludarabine dose is given within 48 hours of graft infusion and to patients with normal renal function.

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Results of Haploidentical Allogeneic Haematopoietic Stem-Cell Transplantation in Patients with Acute Leukaemia: A Single Centre Experience

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Background: Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is a potentially curative treatment for a variety of hematologic malignancies and nonmalignant hematologic disorders. However, only about a third of candidates for allo-HSCT have HLA-matched siblings. For patients who lack HLA-matched siblings, partially HLA-mismatched (haploidentical) related donors are good alternative sources of stem cells for allo-HSCT. In this retrospective, single center study we evaluated safety and efficacy of haploidentical allo-HSCT compared to those of HLA-matched allo-HSCT in patients with acute leukemia.

Methods: A total of 94 acute leukemia patients with a mean age of 37 years who underwent allo-HSCT between June 2010 and November 2012 were analyzed. All patients received Cyclophosphamide (Cy) 50 mg/kg i.v. on days +3 and +4. Pharmacologic prophylaxis of GvHD with cyclosporine-A (CsA) and mycophenolate mofetil (MMF) was not initiated until day +5 to avoid blocking Cy-induced tolerance. All patients received CsA which was initiated at a dose of 400 mg/day, and then adjusted according to the plasma levels. If there was no GvHD, it was tapered off by day +180. In addition to CsA, all haploidentical allo-HSCT recipients received MMF until day +35 at a dose of 1 gr/day.

Results: There were no significant differences in age, sex, type of acute leukemia, disease status up-front HSCT, or transplant characteristics between the groups except a higher median number of stem cells infused in haploidentical group ($p=0.002$). The median follow-up was 194 (range 88-372) days for haploidentical group and 210 (range 105-417) days for HLA-matched group. 98% of the patients engrafted. The median time to neutrophil and thrombocyte engraftments were significantly longer in the haploidentical group compared to the HLA-matched group (neutrophil engraftment; 20 days vs 16 days, respectively, $p= 0.006$) (thrombocyte engraftment; 18 days vs 16 days, respectively, $p=0.015$). The incidence of acute GvHD $>= 2$ was 56% in haploidentical group and 19% in HLA-matched group ($p=0.001$). The incidence of documented viral infections was significantly higher in the haploidentical group compared to the HLA-matched group (42% vs 11%, respectively, $p=0.001$). The relapse rates as well as the overall mortality rates (at 100 days and 1 year) were not significantly different between the two groups.

Conclusion: Our results suggest that haploidentical allo-HSCT is a safe treatment modality in patients with acute leukemia who lack HLA-matched siblings. The major problems are seems to be viral infections and acute GvHD. Future challenges remain in improving post-transplant immune reconstitution and finding the best approach to reduce the incidence and severity of GvHD and infections, while preserving graft-versus-leukemia effect to prevent the recurrence of the underlying disease.

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Post-Transplant Lymphoproliferative Disorder Is Common after Reduced-Intensity ATG Conditioning and Haplo-Cord Transplantation

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