Lymphoid and myeloid immune cell reconstitution after nicotinamide-expanded cord blood transplantation

Omidubicel (nicotinamide-expanded cord blood) is a potential alternative source for allogeneic hematopoietic cell transplantation (HCT) when an HLA-identical donor is lacking. A phase I/II trial with standalone omidubicel HCT showed rapid and robust neutrophil and platelet engraftment. In this study, we evaluated the immune reconstitution (IR) of patients receiving omidubicel grafts during the first 6 months post-transplant, as IR is critical for favorable outcomes of the procedure. Data was collected from the omidubicel phase I-II international, multicenter trial. The primary endpoint was the probability of achieving adequate CD4+ T-cell IR (CD4IR: > 50 × 10^6/L within 100 days). Secondary endpoints were the recovery of T-cells, natural killer (NK)-cells, B-cells, dendritic cells (DC), and monocytes as determined with multicolor flow cytometry. LOESS-regression curves and cumulative incidence plots were used for data description. Thirty-six omidubicel recipients (median 44; 13–63 years) were included, and IR data was available from 28 recipients. Of these patients, 90% achieved adequate CD4IR. Overall, IR was complete and consisted of T-cell, monocyte, DC, and notably fast NK- and B-cell reconstitution, compared to conventional grafts. Our data show that transplantation of adolescent and adult patients with omidubicel results in full and broad IR, which is comparable with IR after HCT with conventional graft sources.

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infections and shorter hospitalization in the first 100 days compared with standard unmanipulated CB transplantation (unCBT) [22, 23].

We and others have recently shown that adequate CD4+ T-cell IR (CD4 + IR) is crucial for favorable survival outcomes [1, 2, 6–8]. Patients with adequate CD4 + IR (>50 × 10^6 CD4+ T-cells/L blood, within 100 days after HCT) had a lower risk of viral reactivation [1], virus-related morbidity and mortality [1], aGVHD-related mortality [27], and relapse-related mortality [6, 8]. In addition, IR of other immune cell subsets, such as natural killer (NK)-cells [28–30], CD8 + T-cells [31–33], and B-cells [34–39], were also related to HCT outcome. As a result of the manufacturing process manipulations and freeze-thaw cycles, the CD3+ dose of the omidubicel NF is lower than in a standard CBT. For example, Purtil et al. reported a median infused viable dose 4.27 × 10^6 CD3+ cells/kg [40]. This is also consistent with the previously published omidubicel experience, indicating that the median CD3+ cell dose from the omidubicel unit was 1.3 × 10^6 cells/kg, which was significantly lower than the median cell dose from the unmanipulated unit of 3.4 × 10^6 cells/kg [41]. The omidubicel CF yields hematopoietic stem and myeloid progenitor cells, but lymphoid cells cannot be detected based on cell surface marker analysis. However, the development of lymphoid cell subsets occurs de-novo from the expanded CD34+ stem and progenitor cells post-transplant [21, 23, 24]. The NF contains mature lymphocytes. The lower CD3+ dose in omidubicel may theoretically be postulated to contribute to a risk of impaired immune recovery following transplantation. Nevertheless, detailed information on IR after transplantation with omidubicel has not yet been reported to date.

We performed in-depth immune monitoring and evaluated plasma protein profiles in patients transplanted with omidubicel grafts in a phase I/II international multicenter study. For this, we developed multicolor flow cytometry panels for harmonized measurements to evaluate the recovery of T-, B-, and natural killer (NK)-cell, monocyte, and dendritic cell (DC) subsets.

**PATIENTS AND METHODS**

**Patients and treatment**

In this phase, I/II multicenter trial, patients with hematologic malignancies received an omidubicel-HCT after myeloablative (MA) conditioning without antithymocyte globulin (ATG), at 11 clinical sites throughout the United States, Europe, and Singapore. Conditioning regimens were applied according to standard protocols, and are described in a previous publication of this trial [23]. The study was approved by the institutional review boards of all participating institutions and the national regulatory authorities. All patients provided written informed consent. Patients were enrolled, and data were collected and registered prospectively only after written informed consent. The study was performed in accordance with the International Conference on Harmonization Guidelines and Good Clinical Practice (ClinicalTrials.gov identifier: NCT01816230).

**Immune monitoring and blood cell samples**

Immune monitoring was performed on peripheral blood samples drawn at 7, 14, 21, 42, 70, and 180 days after infusion of the graft. Absolute leukocyte, lymphocyte, neutrophil, and monocyte cell numbers were measured in fresh EDTA-whole blood. Mononuclear cells were isolated using Fico-II-Paque (BD Biosciences, Sweden) and cryopreserved for later measurements with the use of standardized and validated multicolor flow cytometry panels. The subsets identified were: for T-cells: naïve (CCR7+CD27+CD45RO−CD45RA−), central memory (CCR7+CD27+CD45RO+CD45RA−), effector memory (CCR7−CD27−CD45RO+CD45RA−), Temra (CCR7−CD27−CD45RO−CD45RA+), and Treg (CD4+CD25+CD127dimFoxP3+) [42, 43]. The helper cell phenotypes were based on chemokine receptor expression shown to be associated with Th helper subsets and in this manuscript are referred to as "Th1" (CD4+ CXCR3+CCR4−CCR5−), "Th2" (CD4+ CCR6−CXCR3−CCR4+), "Th17" (CD4+ CCR6+CXCR3+CCR4−IgM+) [42, 43]. B-cells were characterized into immature (CD19+CD24++CD38−IgM−), transitional (CD19+CD24+CD38−IgM−IgD−), follicular (CD19+CD24+CD38−IgM+IgD+), memory (CD19+CD24−CD38−), and plasmablast (CD19+CD24−CD38+IgM+) [44, 45]. For other subsets, markers were as follows: for NK-cells: naïve (CD3−CD56−CD16−) and effector (CD3−CD56−CD16+), for NK T-cells: NKT (CD3+CD56−), invariable NKT (inNKT: CD3+CD56−TCRVbeta1+), TCRvalpha24+ [46, 47], for monocytes: classical (lin-HLA.DR+CD14+CD16−), intermediate (lin-HLA.DR+CD14+CD16+), non-classical (lin-HLA.DR+CD14−CD16+) [48]; and for DCs: conventional (CD1c; lin-HLA.DR+CD14+CD16−CD11c+; available numbers of cells were too low to report DC1 versus DC2) and plasmacytoid (pDC; lin-HLA.DR+CD14−CD16−CD11c−). An overview of the monoclonals used is provided in Supplemental Table 1. Subsets were calculated as the percentage of total evaluable immune cells. Absolute lymphocyte, leukocyte, and monocyte counts were available from standard immune monitoring on fresh material. Absolute numbers of immune cell subsets from in-depth immune monitoring were calculated from total absolute lymphocyte number (for T-, B-, NK-cells) or leukocyte number (for DC).

**Luminex and plasma samples**

Plasma was collected by centrifuging EDTA-whole blood samples, at 0, 1, 7, 14, 21, 42, and 70 days after transplantation. A total of 60 plasma proteins were measured per sample using multiplex immunoassays (Luminex Technol Using Spearman regression. R software (version 4.0.1) and ggplot2 package (version 3.3.3) were used for data analysis and production of graphs [52].

**RESULTS**

In this phase I/II multicenter trial, 36 omidubicel recipients (median age 44, range 13–63 years) were included. Patient characteristics are described elsewhere [23]. Omidubicel cell dose consisted of a median 6.3 × 10^6 CD34+ cells/L blood, and 2.4 × 10^6 CD3+ T-cells/kg of the co-infused negative fraction (following CD133+ selection). Informed consents for in-depth immune monitoring were available from 28 omidubicel recipients. There was no selection bias for these 28 consented patients, based on median age (39 years [13–63]) and median cell dosages of 6.1 × 10^6 CD34+/kg and 2.4 × 10^6 CD3+ T-cells/kg.

**IR after omidubicel transplantation**

Since early adequate CD4+ IR has been related to lower infection-related morbidity and lower overall mortality [1, 3, 7, 53], we evaluated CD4+ IR probability in omidubicel recipients. CD4+ IR was evaluable in 20 patients; not all 28 patients had data on absolute CD4+ T-cell count on two consecutive time points within the first 100 days after HCT. This was either due to death prior to achieving two data points or limited lymphocyte data available to calculate absolute CD4+ T-cell count. Eighteen (90%) achieved successful CD4+ IR (Fig. 1-left). Including all 28 consented patients, adaptive immune cell reconstitution of overall CD4+ (Fig. 1-right), CD8+ (Fig. 2-left), and CD19+ (Fig. 2-right) T-cells, and B-cells (Fig. 3), was observed within the first 6 months after omidubicel transplantation, with a slightly earlier recovery of innate immune cells, including NK-cells (Fig. 4), monocytes (Fig. 5), and DCs (Fig. 6). Especially, the reconstitution of B- and NK-cells was fast compared to other cell subsets, with early high cell counts.
of \( \sim 500 \) and \( \sim 1500 \times 10^6 \) cells/L, respectively, within the first month after transplantation.

**In-depth immune monitoring after omidubicel transplantation**

The recovery of T-cell subsets during the first 6 months after omidubicel transplantation is broad and full in terms of the presence of effector and central memory CD4+ and CD8+ T-cells, gamma-delta T-cells, Tregs, Th2, Th1, and Th17 cells (Figs. 1 and 2, Supplemental Fig. 1). Within total CD3+ T-cells, relative amounts of gamma-delta T- (1–4%), CD8+ (24–36%), and CD4+ (61–74%) T-cells are normalized within the first month after transplantation. Both CD8+ and CD4+ T-cell recovery are predominately effector memory T-cells (\( \sim 50\% \)), although relatively high naive T-cell counts within the first month after omidubicel transplantation are observed compared to later time points (\( \sim 20\% \) versus \( \sim 7\% \)). Furthermore, the second most predominant subsets are Temra (29–55%) in CD8+ T-cell recovery, and central memory T-cells (19–24%) in CD4+ reconstitution. In addition, although absolute counts of Tregs, as well as Th2, Th1, and Th17, remain low, the
relative amount of Tregs in some patients (~5% [range; 1927%] of total CD4+ T-cells) might be slightly higher than in healthy adults (2–3% of CD4+ T-cells) [54]. B-cell reconstitution starts with relatively high amounts of memory B-cells during the first weeks after transplantation, followed by increased percentages of follicular B-cells (Fig. 3). NK-cell recovery starts with relatively high naive NK-cell counts within the first weeks, after which generally more effector NK-cells are observed (Fig. 4), with only low amounts of NKT and iNKT cells. Furthermore, monocyte recovery starts with relatively high amounts of intermediate monocytes in the first month after omidubicel transplantation, after which most monocytes are classical monocytes, with lower amounts of intermediate and non-classical monocytes (Fig. 5). DC reconstitution during the first year after omidubicel transplantation consists of primary cDCs and few pDCs (Fig. 6).

**Plasma protein profiles in relation to immune subset reconstitution**

We evaluated correlations between plasma proteins at days 0, 1, and 7 with immune subset reconstitution at days 21, 42, 70, 100, and 180 in all 28 patients. The correlations between plasma proteins measured at day 1 and IR at day 21–70 were most robust, with the least missing data, and best represented the overall observations (Fig. 7). An overview of all plasma protein profiles over time after transplantation is provided in Supplemental Fig. 2.1–2.4. Interestingly, plasma IL15 concentration followed a similar recovery trend compared to the NK-cell counts, with a peak observed after one week for IL15 and around 6 weeks for NK-cells (Fig. 4 and Supplemental Fig. 2.1). In accordance with this observation, we found an, albeit weak, correlation between IL15 at day 1 and NK-cell counts at days 21, 42, and 70 (Fig. 7). Furthermore, increased IL2 concentrations correlated with counts of almost all T-cell subsets only, while increased sPD1 was correlated to increased CD8+ T-cell and to decreased CD4+ T-cell subset counts. IL22 is positively correlated with B-cell subset recovery. We further observed that ST2 was positively correlated with adaptive immune cell counts (T- and B-cell subsets), but negative correlations were found with innate immune cell recovery (DC-, monocyte, and NK-cell subsets). In turn, LAG3, CD40L, APRIL, VEGF, Elastase, S100A8, and M-CSF were positively correlated to innate immune cell recovery, and negatively with adaptive immune cell counts.

**DISCUSSION**

This unique international, multicenter, in-depth immune monitoring study reveals rapid and robust IR after transplantation with omidubicel. The probability of early CD4+ IR was high, overall CD4+ and CD8+ T-cell, monocyte, and DC reconstitution were observed, and recoveries of B-cells and NK-cells were strikingly fast after omidubicel transplantation. Together with the recently reported clinical outcome of this phase I/II study, our findings indicate that transplantation with omidubicel is not only feasible in terms of potent engraftment [23] but also results in a full and broad IR.

The fast NK- and B-cell reconstitution after omidubicel transplantation in comparison to other graft sources, might be related to an intrinsic characteristic of cord as previously described in unmanipulated-CBT recipients [10, 55, 56]. The higher number of progenitor cells obtained with omidubicel expansion may also contribute to the enhanced NK- and B-cell reconstitution, although as previously discussed, the cultured cells do not contain mature lymphocytes or NK cells, and the non-cultured cells contain a reduced number of cells compared to a standard CB unit [25, 57]. It would, therefore, be interesting to evaluate if fast NK-cell recovery after omidubicel transplantation would translate to a lower relapse risk or viral reactivation incidence as observed after unmanipulated-CBT [58, 59]. These analyses must, however, be performed in a comparative setting. In addition, improved NK-cell and NKT-cell recovery have been associated with improved overall survival and risk of infection [3, 60], as well as reduced aGvHD risk specifically for the CD56bright NK-subset [28]. Also, early reconstitution of Tregs seems to protect against aGvHD development [61–63], and a Th17/Treg ratio <1 correlated favorably with aGvHD development and severity [63]. Therefore, it is of high clinical interest to further study in-depth IR, in terms of immune cell subsets, to correlate IR after omidubicel transplantation to the outcome and subsequently find possible biomarkers that can predict outcome in future omidubicel recipients. The current international multicenter phase III trial allows for further IR studies with an increased number of patients, and inclusion of a randomized control cohort of single and double CBT, and may allow correction for covariates that can affect IR (such as age, chemotherapy dosage, GvHD, and steroid-treatment) [9, 64–66] in multivariate analyses for more robust statistical testing.

Our in-depth immune monitoring after omidubicel transplantation also shows robust reconstitution of a broad range of immune cell subsets of CD4+ and CD8+ T-cells, Tregs, gamma-delta T-cells, as well as monocytes, conventional and plasmacytoid DCs. The potent recovery of in particular CD4+ T-cells (>50 × 106 CD4+ T-cells/L blood within 100 days), might be of interest for outcome after omidubicel transplantation since recent evidence suggests that adequate CD4+ IR is related to lower morbidity and mortality after HCT [1–3, 7, 53]. Firm conclusions on CD4+ IR potency, and its’ effect on the outcome, as well as on the breadth of IR in omidubicel recipients are limited by the small number of the evaluated cohort. Nevertheless, these findings indicate that nicotinamide exposure seems to preserve the high IR-potential of CB-grafts, and the ability of the stem and progenitor cells to reconstitute the full range of immune cell subsets in the periphery.

Plasma proteins are currently in the picture as potential biomarkers for outcome after HCT. For instance, early protein...
profiles of ST2, REG3α, TNFR1, and IL-2Ra were recently reported as predictors for aGvHD severity [67, 68]. In our report, we are the first to show that plasma protein profiles in the first week after omidubicel transplantation correlate with IR data in the weeks thereafter. In particular, we found indications that increased early IL15 plasma concentrations can be related to the fast NK-cell recovery after omidubicel transplantation. IL15 is known to activate NK-cells and improve their function [69, 70]. In addition, we found that IL22 correlates to B-cell reconstitution, while IL22 (produced by immune cells and mucosal epithelial cells) has been linked to B-cell function [71, 72]. Interestingly, we observed that some plasma proteins, such as ST2, are positively related to

Fig. 4 NK- and NKT-cell reconstitution after omidubicel transplantation. (Upper) Smoothened LOESS-curve with 95% confidence interval (gray area), with dots showing the data points, for absolute NK-cell counts following omidubicel transplantation. Each dot represents a single data point for a single patient. (Middle) Pie-charts of NK-cell subsets as percentages of NK-cells; effector and naive NK-cells, at 7–14, 21, 42, 70, and 180 days after transplantation. (Lower) Smoothened LOESS-curves of NKT- and iNKT-cell recovery after omidubicel transplantation.
adaptive immune cell recovery, but negatively to innate immune cell subsets. The role of the ST2 pathway in both adaptive and innate immune cell function is reviewed elsewhere [73]. In turn, higher concentrations of proteins as CD40L, APRIL, and M-CSF, are related to increased innate cell counts and decreased adaptive immune cell counts. These proteins have all been linked to innate as well as adaptive immunity [74–77]. Nevertheless, due to the sparseness of the datasets for these multilayer analyses, we cannot draw strong conclusions from these observations. For this, these relations between plasma proteins and immune subset recovery should be evaluated in larger prospective cohorts, including more patients and more HCT-graft types. In addition,
while we focused on the relationship between plasma protein profiles and IR, it is of high interest to further relate this to outcome in a future study with more patients and data.

This study shows that omidubicel transplantation in adolescent and adult patients results in fast and diverse IR that is comparable to reference cohorts of conventional unCBT and BMT at the least. Future studies are needed to further evaluate how IR relates to the outcome, and especially if the enhanced NK-cell and B-cell IR after omidubicel transplantation result in favorable outcomes for patients with hematopoietic malignancies. The results of the present study show that omidubicel transplantation is a potent alternative cell source for HCT in adolescent and adult patients.

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COMPETING INTERESTS

TF, EGC, and UG are affiliated at Gamida Cell Ltd. These authors had no role in gathering the data or the analyses performed in this manuscript.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-021-01417-4.

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