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Efficacy of CD 25 blockade as targeted adjuvant therapy in the prevention of GVHD in pediatric stem cell transplant recipients

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Project and bibliography

Prevention of Graft-versus-host disease (GVHD) in patients treated with allogeneic stem cell transplantation (SCT) can reduce morbitity and mortality. Considering the major role of activated T cells in pathophysiology of GVHD, monoclonal antibodies against interleukin-2 receptor a chain (anti-CD25) were used for reducing T cell activation and proliferation in patients after allogeneic SCT. First, we assessed the safety in 11 patients (n=11) and CD25 blockade (n=9) under treatment with chimeric or humanized anti-CD25 (ch/anti-CD25) in pediatric allogeneic SCT. Ch/anti-CD25 (1 mg/kg) was given 6 hours before SCT and on day 4 (d+4), +28, +56 and +84 after SCT and was well tolerated. 6/11 patients completed the treatment protocol. 3/6 patients showed complete CD25 blockade (<1% CD25+ T cells by FACS detected in peripheral blood) until d+100. In the other 3 patients duration of CD25 blockade was 13 ± 2.2, 16 ± 2.5 and 23 days after last antibody application. Patients suffering from chronic GVHD and showing CD25+ cells received another 2 to 5 anti-CD25 applications after d+100. The mean time of CD25 blockade in these patients ranged from 21 ± 3 days [19; 23] to 55 ± 11 days [46; 64] 95%CI (mean, SD, [95%CI]). Next, we compared the incidence of GVHD, relapse and survival in 34 patients receiving allogeneic stem cell transplants under treatment with either prophylactic ch/anti-CD25 (group A, n=11) or prophylactic murine (m/anti-CD25, group B, n=13) or without anti-CD25 (group C, n=10) after SCT. The incidence of acute GVHD grade II-IV in ch/anti-CD25 receiving patients was not lowered compared to patients receiving murine or no anti-CD25 (0.6 vs. 0.54 vs. 0.4). Moreover, a significantly higher incidence of limited but not extensive chronic GVHD was seen in group A in comparison to group B (0.75 vs. 0.22; p=.036) but not in comparison to group C. The higher incidence of limited chronic GVHD was probably caused by the higher rate of mature T cells transplanted with the peripheral blood in group A as compared to bone marrow in group B and C. Patients in group A had earlier engraftment possibly due to the same reason compared with group B and C (14 vs. 23 vs. 20.5 days; p<.015). Although probability of overall survival (0.22 vs. 0.54 vs. 0.6) and leukemia free survival (EFS, 0.11 vs. 0.54 vs. 0.6) was not significantly different between all groups, we observed a trend towards superior EFS in groups B and C. More cumulative chemotherapy in group B and C patients due to longer treatment before transplant as well as more immunosuppressive treatment due to chronic GVHD in group A may have contributed to this trend. Our findings may also suggest a role of CD25 positive T cells in the balance of achieving tolerance and leukemia control. The complex role of CD25 in regulatory and effector T cells of allo- and leukemia recognition warrants further investigation.

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Lebenslauf

Persönliche Erklärung

Danksagung

Abbreviations

A	group A patients, treated with humanized or chimeric anti-CD25
aGVHD	acute graft-versus-host disease
AICD	activation-induced cell death
AL	acute leukemia
ALL	acute lymphocytic leukemia
AML	acute myeloic leukemia
ANC	absolute neutrophil count
anti-CD25	monoclonal antibody against interleukin-2 receptor a chain
anti-CD52	monoclonal antibody against CD52 receptor, (used therapeutically to deplete T cells)
APCs	antigen presenting cells
ATG	antithymocyte globuline
B	group B patients, treated with murine anti-CD25
Bas	basiliximab, a chimeric monoclonal antibody against CD25
BFM-study	Berlin-Frankfurt-Münster-study
BM	bone marrow
BMT	bone marrow transplantation
BT563	inolimomab, a murine monoclonal antibody against CD25
Bu	busulfan
C	group C patients, without CD25 antibody treatment
c-ALL	acute lymphocytic leukemia, common type
CB	cord blood
CBSC	cord blood stem cells
CBT	cord blood transplantation
CD	clusters of differentiation
CD3	T cell receptor complex
CD3+	CD3 positive
CD25	interleukin 2 receptor a chain, Tac
CD25+	CD25 positive
CD4+CD25+	CD4 and CD25 double positive
CD122	interleukin 2 receptor ß chain
CD132	interleukin 2 receptor ? chain
CDRs	complementarity determining regions
cGVHD	chronic graft-versus-host disease
ch/anti-CD25	chimeric or humanized anti-CD25

chi-square	chi-square test
CI	confidence interval
COALL	cooperative ALL study
CR	complete remission
CSP	cyclosporine A
CTL	cytotoxic T cells
CTLA-4	high affinity receptor for costimulatory molecules on T cells
Cy	cyclophosphamide
d+x	day x from allogeneic transplantation
Dac	daclizumab, a humanized monoclonal antibody against CD25
D	donor
DOC	death of complication
DOD	death of disease
EFS	event free survival, leukemia free survival
Eto	etoposide
F	female
FAB	French-American-British classification of acute myelocytic leukemia
FACS	fluorescence-activated cell sorter
FAS	FAS receptor, member of the TNF receptor family
FITC	fluoresceinisothiocyanat
G-CSF	granulocyte-colony stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage-colony stimulating factor
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia effect
Gy	gray
HLA	human leukocyte antigen
IFN	interferon
IL	interleukin
IL-2	interleukin-2
IRB	internal review board
i.v.	intravenously
IgG1	immunoglobulin G1
IL-2R	interleukin-2 receptor
IL-2Ra	interleukin-2 receptor a chain
KGF	keratinocyte growth factor
log-rank	log-rank test

LPS	lipopolysaccharide
M	male
mab	monoclonal antibody
m/anti-CD25	murine anti-CD25
M-BCR/ABL	rearrangement of t(9;22)
MDS	myelodysplastic syndrome
Me	melphalan
MHC	major histocompatibility antigens
mHC	minor histocompatibility antigens
MMF	mycophenolate-mofetil
MØ	monocyte
MTX	methotrexate
MUD	matched unrelated donor
n	number of patients
NK	natural killer cells
NR	non response
OAS	overall survival
PB	peripheral blood
PBSC	peripheral blood stem cells
PE	phycoerythrin
PPR	prednisone poor response
PRED	6-methylprednisolone
PSC	peripheral stem cells
PUVA	psoralene and ultraviolet A radiation
R	recipient
RAEB	refractory anemia with excess blasts
SCT	stem cell transplantation
SD	standard deviation
T-ALL	acute lymphocytic leukemia, T cell type
TBI	total body irradiation
TCR	T cell receptor
Th1	T helper-1 cell
TNF	tumor necrosis factor
UCB	unrelated cord blood
UPN	unique patient number
VOD	venoocclusive disease
yrs	years

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