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Intravenous Monoclonal Antibody (BT 5/9) for the Treatment of Acute Graft-versus-Host Disease

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Acute graft-versus-host disease (GvHD) is a common complication of allogeneic bone marrow transplantation (BMT), despite the use of prophylactic methotrexate or cyclosporin A (CyA) [1]. Severe GvHD (grade III-IV) occurs in 15–20% of allogeneic BM recipients, and is associated with a high (over 50%) mortality rate [1].

Treatment of severe GvHD includes antilympho-cytic globulin [2], high-dose methylprednisolone [3] and, recently, pan-T monoclonal antibodies (Mab) [4,5].

The risk of such treatments is mainly immunosuppression, which has been associated with the occurrence of non-Hodgkin lymphoma in the case of OKT3Mab [5].

We are now reporting a pilot study designed to test the efficacy of a helper-T Mab (BT 5/9) for the treatment of severe GvHD. BT 5/9 is an IgG3 which does not bind complement; it reacts with 15–20% of peripheral blood T cells in normal individuals and identifies helper cells in assays for in vitro Ig synthesis [6]. In addition, removal of BT 5/9+ cells from a mixed leukocyte reaction prevents both proliferation and generation of cytotoxic T lymphocytes (CTL) from BT 5/9- cells [7]. Patients were all recipients of an HLA identical allogeneic BMT. All patients, except UPN 999 who was given methotrexate according to the Seattle protocol [1], received CyA for GvHD prophylaxis, as described elsewhere [8], and were diagnosed as having severe GvHD according to published clinical criteria [1]. They were all treated with BT 5/9, after proving refractory to steroids (UPN 77, 78, 85, 90, 92, 97, 100), or ALG (UPN 999). The latter patient

1 Supported by C.N.R. (P.F.O.) CT 84.00661.44.

was grafted in another unit and treated with BT 5/9 in the Department of Hematology of Cagliari. All patients received 2 mg of BT 5/9 per m² per day on each of 5 consecutive days, after premedication with anti-histamines and steroids (0.5 mg/kg of prednisolone). Relevant clinical data are shown in table I.

The proportion of circulating BT 5/9+ T cells dropped from 3–35% on day 0 of treatment to 1–10% on day 5 (table I).

The mean grading of GvHD was 2.7 (range II-III) on day 0 of treatment, 2 on day 14 (range O-III) and 1.4 on day 30 (range O-III) (table I). There were 4 complete responders, 2 partial

responders and 2 refractory patients. Two patients went on to develop mild chronic GvHD, one developed severe cGvHD and requires intensive immunosuppressive treatment. Five patients are surviving 12–19 months post-treatment. Three patients died of GvHD and infection on days 54, 37, 29 from treatment. The 1-year survival of these patients is currently 63%, with all surviving patients alive at least 1 year post-treatment (fig. 1): this is better than our previous experience with high-dose methylprednisolone in similar patients [3]. Complications included chills and fever in 2 patients immediately after the intravenous administration of BT 5/9, and Candida infections in 5 of 8 patients. Such infections were disseminated in 3 patients and a major cause of death in two.

In conclusion, treatment with this Mab is well tolerated with acceptable immediate adverse reactions. Candida infections are a problem, possibly due to im-munosuppression. A significant proportion of patients showed improvement of GvHD, and 63% survive 1 year later. We have not as yet observed the occurrence of malignant lymphomas.

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Table I. Relevant clinical data of 8 patients

UPN

Age

Sex

Diag-

Days of

Grading GvHD

% positive cellsb

Re-

Sur-

Cause of death

years

nosis3

treat-

sponse0

vival

present status

ment from

0 daysd

14

30 daysd

Epos.

BT 5/9 pos.

monthi

days

BMT

0 daysd

5 daysd

0 daysd

5 daysd

17
F
SAA
+ 37
IIsg
II
I
35
50
33
11
CR
19 +
well
78
19
F
ALL
+ 61
IIsg
II
II
30
nt
nt
17
nt
PR
2
GvHD + Candida
85
5
F
ANLL
+ 31
IIsg
III
III
64
64
23
10
REF
1
GvHD + Candida
90
18

M
ALL
+ 83
IIIsIg
II
ne
20
nt
3
nt
PR
1
GvHD + Infece
92
7
F
ALL
+ 26
IIIsI
II
II
23
31
10
1
REF
14 +
cGvHD(++)e
97
11
M
ALL
+ 14
Hsg
0
0
70
60
35
20
CR
12 +
well
100
21
M

SAA

+ 30

II⁺slg

III

I

nt

32

22

2

CR

12 +

well-cGvHD(+)^e

999

2

F

THAL

+ 210

II⁺slg

II

I

nt

nt

nt

nt

CR

12 +

well-cGvHD(+)^e

^a SAA = Severe aplastic anemia; ALL = acute lymphoblastic leukemia; ANLL = acute non-lymphoid leukemia; THAL = thalassemia major.

^b E pos., BT 5/9 pos. = Peripheral blood cells rosetting with sheep red blood cells (E pos.) or with BT 5/9 coated ox-erythrocytes (BT5/9 pos.).

^c CR = Complete response; PR = partial response; REF = refractoriness.

^d Days from treatment.

^e Candida infections: pneumonia (UPN 78), candidemia (UPN 85); Infec (UPN 90) = disseminated enterococcus; cGvHD = chronic

GvHD: (+) mild, (+ +) severe.

100 90-

80-

70

60

50-

40

30

20

10

Months from treatment

Fig. 1. Survival of 8 patients with severe GvHD treated with a monoclonal antibody (BT 5/9).

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