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TNI in graft-versus-host disease

Total nodal irradiation in patients with severe treatment-refractory chronic graft-versus-host disease after allogeneic stem cell transplantation: Response rates and immunomodulatory effects

Anke H. Hautmann [a,*], Daniel Wolff [a], Inken Hilgendorf [b,1], Ute Fehn [a], Matthias Edinger [a], Petra Hoffmann [a], Wolfgang Herr [a], Oliver Kölbl [c], Barbara Holler [a], Daniela Sporrer [a], Ernst Holler [a], Matthias G. Hautmann [c]

[a] Department of Internal Medicine III (Hematology and Oncology), University Medical Center of Regensburg; [b] Department of Internal Medicine (Hematology and Oncology), University Hospital of Rostock; and [c] Department of Radiotherapy, University Medical Center of Regensburg, Germany

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ABSTRACT

Background and purpose: The use of total nodal irradiation (TNI) has been reported as an immunomodulatory therapy for different diseases including chronic graft-versus-host disease (cGVHD).
Material and methods: We retrospectively analyzed 13 patients with treatment-refractory cGVHD receiving TNI with 1 × 1 Gy from 2001 to 2014. In 10 of 13 patients immunomodulatory effects of TNI were measured.
Results: At time of TNI all patients had severe cGVHD (involving the skin: $n = 12$), fascia ($n = 6$), oral mucosa ($n = 8$), eye ($n = 8$), and lung ($n = 5$). Nine of 13 patients had corticosteroid-refractory cGVHD. In 7 of 13 patients (54%) a partial response (PR) could be achieved. In 3 patients (23%) cGVHD manifestations remained stable, 2 patients progressed. One patient was not evaluable due to follow-up <1 month. At 3 months after TNI, best responses could be achieved in skin, and oral involvement including steroid sparing activity. TNI was well tolerated with adverse effects limited to reversible thrombocytopenia and neutropenia. Immunomodulatory effects on peripheral blood cells could be demonstrated including an increase of CD4+ T cells in the group of responders.
Conclusions: TNI represents an effective immunomodulating therapy in treatment-refractory cGVHD.
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Corticosteroid-refractory severe cGVHD is a major cause of late morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and is difficult to manage [1]. First-line treatment of cGVHD consists mainly of prednisone with a starting dose of 1 mg/kg/day, often combined with a calcineurin inhibitor (CNI) [2]. A number of second-line therapies exist, including mycophenolate mofetil, mTOR inhibitors, extracorporeal photophoresis and monoclonal antibodies but none of them is approved in cGVHD and evidence is limited to case series or phase II trials [3]. Chronic GVHD requiring long-term immunosuppressive treatment is a risk factor for infections, organ failure and secondary malignancies and is associated with a significant impairment in quality of life [3,4]. The efficacy of these therapies varies and is often limited, especially in patients with deep sclerosis of the skin.

TNI has a long history not only for treatment of lymphoma but also as an immunosuppressive therapy [5–9]. In the 70s, TNI was developed as a curative treatment for Hodgkin's lymphoma. Immunomonitoring during treatment and beyond showed a faster recovery of CD8+ than CD4+ T cells with immunomodulating potential [10]. In the 80ties, TNI was applied in patients with autoimmune diseases (e.g. rheumatoid arthritis and multiple sclerosis). However, whereas notable responses could be achieved with high total doses of up to 20 Gy (20 × 1 Gy, 5 times/week) such treatment also caused severe toxicity [7]. By decreasing the total dose to 8 Gy (10 × 0.8 Gy, twice/week), e.g. in the treatment of organ rejection or bronchiolitis obliterans syndrome after organ transplantation toxicity could be reduced, but still remained significant [11,12].

Recently, the dosage was gradually reduced to 1 × 1 Gy with considerably less toxicity and still sustained immunomodulatory effects [8]. In the setting of cGVHD, usually TNI with 1 × 1 Gy is

* Corresponding author at: Department of Internal Medicine III, University Medical Center of Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany.
E-mail address: anke.hautmann@ukr.de (A.H. Hautmann).
[1] Current affiliation: Hematology/Oncology, Jena University Hospital, Jena, Germany.

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used. For TNI as well as for total lymphoid irradiation (TLI) the main targets are the lymph node areas and the lymphatic tissue. As the term TLI is often used for conditioning regimes, the low dose irradiation for cGVHD is named as TNI in the Departments of the authors – although the target volume is very similar. A few retrospective analyses in patients with severe cGVHD treated by TNI with 1×1 Gy could demonstrate remarkable response rates in patients with skin and hepatic involvement [13] as well as in patients with fasciitis and oral cGVHD [14–16]. Devillier et al. reported nine patients with cGVHD receiving 2 sessions of TNI with 1 Gy, respectively, without noteworthy toxicity but still efficient response rates. Therefore, TNI has been considered as a safe and efficient option in the treatment of refractory GVHD, allowing a significant tapering of steroids in most cases [13].

Immunomodulatory effects of TNI as conditioning regimen before HSCT have been reported in murine models as well as in clinical studies [5,6,8,18–20]. To our knowledge, measurement of immunomodulatory effects has not been performed in patients with cGVHD treated with TNI, so far.

The aim of our analysis was to investigate the feasibility, the response rates and immunomodulatory effects of TNI in patients with severe cGVHD.

Patients and methods

From July 2001 to April 2014, a total of 13 patients received TNI treatment due to severe chronic GVHD. Eleven patients were treated at the University Medical Center of Regensburg, Germany, and two patients were treated at the University Hospital of Rostock, Germany. Patient characteristics are shown in Table 1. All patients presented with severe steroid-dependent or steroid-refractory cGVHD.

All patients provided informed consent to undergo treatment. In addition, ten patients receiving treatment at the University of Regensburg provided informed consent to assess immunoregeneration of peripheral blood cells (IRB [Institutional Review Board] approval number: 02/220, University of Regensburg).

Diagnosis of cGVHD and assessment of organ involvement was performed according to the National Institutes of Health (NIH) consensus criteria [21]. The NIH consensus criteria standardize the criteria for diagnosis of cGVHD and propose a new clinical scoring system (0–3) that describes the extent and severity of cGVHD for each organ or site, taking functional impact into account. The consensus proposes new guidelines for global assessment of cGVHD severity that are based on the number of organs or sites involved and the degree of involvement in affected organs (mild, moderate, or severe) [21]. Data were collected from the transplant center's database and chart review, respectively (last follow-up data on the 13.07.2015). Three patients with cGVHD who developed GVHD before 2005 were reclassified according to the NIH criteria by a chart review. For assessment of organ involvement the "chronic GVHD assessment form" according the NIH consensus criteria was used on a regular basis [21].

Table 1
Patient characteristics.

Characteristics	cGVHD ($n = 13$)
Male, *n* (%)	7 (54%)
Female, *n*	6 (46%)
Age in years, median (range)	48 (18–63)
Diagnosis, n (%)	
AML[1]	4 (31%)
ALL[2]	1 (8%)
OMF[3]	2 (15%)
NHL[4]	5 (38%)
CML[5]	1 (8%)
Donor type, n (%)	
Matched-unrelated donor (MUD)	6 (46%)
Matched-related donor (MRD)	7 (54%)
Preparative conditioning regimes, n	
RIC[6]	12 (92%)
MAC[7]	1 (8%)
Conditioning regimen with TBI	3 (23%)
Prior exposition to radiotherapy	1 patient: TBI 12 Gy and 24 Gy full cranial irradiation 1 patient: 4 Gy TBI 1 patient: 2 Gy TBI
Grade of prior acute GVHD, n (%)	
I	2 (15%)
II	9 (69%)
III–IV	0 (0%)
Karnofsky performance status at TNI in median (range)	70% (30–90%)
Type of onset of cGVHD, n (%)	
de novo	2 (15%)
Quiescent	10 (77%)
Progressive	1 (8%)
Type of cGVHD, n (%)	
Classic	10 (77%)
Overlap-syndrome	3 (23%)
cGVHD maximal grade before TNI, n (%)	
Severe	13 (100%)
Indication for TNI, n (%)	
Steroid-dependent cGVHD	4 (31%)
Steroid-refractory cGVHD	9 (69%)
Main organ manifestation of cGVHD at TNI, n (%)	
Skin	12 (92%)
Oral	8 (62%)
Ocular	8 (62%)
Liver	2 (15%)
Gut	1 (8%)
Lung	5 (38%)
Genital	2 (15%)
Fasciitis	6 (46%)
Duration of GVHD before TNI in days, median (range)	838 (254–3910)
Time point of TNI after allo-SCT in days, median (range)	1235 (420–4015)

[1] AML = acute myeloid leukemia.
[2] ALL: acute lymphoblastic leukemia.
[3] OMF = osteomyelofibrosis.
[4] NHL = non hodgkin lymphoma.
[5] CML = chronic myeloid leukemia.
[6] RIC = reduced-intensity conditioning.
[7] MAC = myeloablative conditioning.

TNI technique

All patients were treated with a linear accelerator (Siemens Primus® or Electa Synergy®) using 6 MV Photons. Opposing fields shielding the lungs were applied. Patients were irradiated from bony palate to knee joint including the arms. 1 Gy was delivered to the abdomen midline in one fraction with a dose rate of 100 cGy per minute.

Flow cytometry

Whole blood was drawn into standard ethylenediaminetetraacetic acid (EDTA)-containing collection tubes and erythrocytes were lysed before staining of peripheral blood cells for 15 min at 4 °C with the following antibodies at optimal concentrations. CD3-FITC (SK7), CD8-PE (SK1), CD4-PerCP (SK3), CD25-APC (2A3), CD45RA-FITC (L48), CD31-PE (L133.1), CD62L-PE (SK11), CD45RA-APC (HI100), CD16-PE (B73.1), CD14-PerCP (MΦP9), CD56-APC (N-CAM 16-2), CD27-FITC (L128), IgD-PE (IA6-2), CD19-PerCP (SJ25C1), IgM-APC (G20-127), CD21-PE (B-Ly 4), CD40-APC (5C3), Lineage-FITC (CD3 = SK7, CD14 = MΦP9, CD16 = 3G8, CD19 = SJ25C1, CD20L27, CD56 = NCAM16-2),