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Title: NEUROLOGICAL COMPLICATIONS IN ADULT ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS: RESULTS FROM A RETROSPECTIVE MULTICENTRE STUDY.

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Text: **Background:** Patients undergoing allogeneic hematopoietic stem cell transplant (HSCT) are exposed to a number of neurological complications that may be related to drugs, infections, metabolic alterations, cerebrovascular events and immune-mediated disorders including myositis, myasthenia gravis, Guillain-Barrè-like demyelinating polyneuropathy and central nervous system (CNS) manifestations of graft versus host disease (GVHD). The multifactorial etiology of neurological complications in HSCT patients makes diagnosis difficult. However a timely and rigorous characterization of such complications should be obtained in the attempt to avoid fatal outcomes or long-term effects. Data regarding neurological complications in HSCT patients derives from small series and varies largely in respect to incidence and severity. Aim of this study is to describe incidence, characteristics and outcome of neurological complications in a large series of consecutive HSCT patients.
Methods: Data were retrieved from medical records of 777 patients transplanted from January 2007 to January 2017 in 3 Italian centres. Complications affecting either central or peripheral nervous system were classified based on their etiology (Maffini et al. Biol Blood Marrow Transplant. 2017;23:388-397) and time of onset (from days 0 to 30, 30 to 120, 120 to 180, 180 to 365, and post day 365).
Results: Overall 34 [median age: 51.5 (19-66) years; F/M: 11/23; Caucasian 31] of the 777 patients analysed (4.4%) presented neurological complications. Among these patients, 19 (55.8%) received a reduced-intensity HSCT, 15 (44.2%) a myeloablative HSCT. Donors were matched related in 10 (29.4%) cases, haploidentical in 2 (5.9%), and matched or mismatched unrelated in 22 (64.7%). Neurological complications were immune-mediated in 11/34 cases (32.3%), infection-related in 9 (26.5%), drug-related in 5 (14.7%), relapse-related in 5 (14.7%), cerebrovascular in 3 (8.8%), and due to a CNS neoplasia in 1 (2.9%). The median time from HSCT to neurological symptoms appearance was 4.7 (0-43.7) months (approximately 141 days). Fourteen patients (41.2%) presented CMV reactivation and 13 (38.2%) were receiving treatment for GVHD at the onset of neurological symptoms. Three (75%) of the 4 drug-related neurological toxicities that occurred within day 30 were observed in patients of Asian (2) and African (1) ethnicity. Details on neurological complications according to etiology and time of onset are depicted in Figure 1.

COMPLICATIONS	0-30 (days)	30-120 (days)	120-180 (days)	180-365 (days)	post-365 (days)
Immune-mediated		6 [GVHD]*	2 [GVHD]**	1 [GVHD]***	2 [GVHD]****
Infection-related	1 [*Fusarium*]	1 [virus unspecified]	1 [*Toxoplasma*] 2 [*JC virus*]	1 [*Toxoplasma*]	1 [*P. meningiditis*] 2 [mycotic unspecified] 1 [*Varicella Zoster virus*]
Drug-related	3 [Cyclosporin] 1 [Busulfan]	1 [Cyclosporin]			
Cerebrovascular		1 [unspecified]	1 [unspecified]		1 [hemorragic]
Disease relapse			1 [AML]	2 [AML] 2 [ALL]	
CNS malignancy					1 [gliobastoma]

*demyelinating disease 1, immune-mediated encephalopathy 2, immune-reconstitution inflammatory syndrome 2, unspecified 1; **unspecified; ***unspecified; ****unspecified 1, Guillan-Barrè like syndrome 1.

[01302] Figure 1. Classification of neurological complications according to etiology and time of onset.

Thirteen of 34 patients (38.2%) died due to the neurological complication (relapse of disease 4, immune-mediated 3, infection-related 2, drug-related 2, cerebrovascular 1, CNS malignancy 1) with a median time from symptoms onset to death of 2.3 (0.2-22.4) months. Among the 21 patients who survived, 2 (9.5%) are currently presenting long-term effects (GVHD-related tetraplegia and sensitive neuropathy, respectively).
Conclusions: Although affecting a limited number of patients, in our series neurological complications were associated to a significant mortality and severe long-term disabilities. Multicentre prospective studies using a common classification system are awaited in order to identify the real incidence and risk factors of neurological complications in HSCT patients.
Conflict of interest: The authors of this abstract have nothing to disclose

Keywords: neurological complications, allogeneic hematopoietic stem cell transplant, early and late effects

Preferred