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Overlap cGVHD: proposal of a prospective GITMO study

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Disclosures of Jacopo Mariotti

No conflict of interests to disclose

A PROSPECTIVE TRANSLATIONAL NON-INTERVENTIONAL STUDY IN PATIENTS DEVELOPING OVERLAP GVHD: INCIDENCE, RESPONSE RATE, OUTCOME AND BIOLOGICAL CORRELATIONS

Promoter: GITMO
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Primary Objective

The primary objective is to improve the understanding of the “overlap syndrome”, a particular subtype of GVHD, characterized by a high degree of uncertainties concerning both diagnosis and treatment due to the simultaneous presence of acute and chronic GVHD features. In particular, the real word incidence of this disease is not well known.

↓

Primary Endpoint

Identify the incidence of the overlap GVHD, relative to the chronic GVHD incidence, at 1 year after HSCT

Overlap GVHD: real world incidence
Background

Historical studies:

- Pidala J et al → retrospective study on 427 patients with cGVHD, →352 (77%) had overlap signs (BBMT 2012)
- Moon JO et al → retrospective study on 317 patients with cGVHD, →173 (54%) had overlap signs (BBMT 2014)

More recent studies:

- Langer R et al → prospective study on 317 adult and pediatric patients: 83.2% presented with signs of classic cGVHD, whereas overlap syndrome was diagnosed in 16.8% (n=20) of cases (Front Immunol 2023)

- Gorfinkel L et al → secondary analysis of data from the prospective ABA2 trial (N=185) →Of 92 patients who developed cGVHD, 35 were classified as overlap chronic GVHD (38%) (BBMT 2024)

Overlap GVHD-Definition

Definitions:

“…..simultaneous presence of acute and chronic GvHD features»
(Schoemans E, BMT 2018)

«The term “overlap” refers to the presence of 1 or more acute GVHD manifestation in a patient with a diagnosis of chronic GVHD. Manifestations of acute GVHD can be present at initial diagnosis of chronic GVHD or can develop after the diagnosis of chronic GVHD and may recur with or without resolution of prior chronic GVHD manifestations» (Jagasia MH, BBMT 2015)

Overlap GVHD: Diagnosis Proposal

Overlap GVHD definition proposal

1) patients developing aGVHD associated with at least 1 organ with diagnostic/distinctive features of cGVHD within 30 days from diagnosis

2) patients developing cGVHD associated, within 30 days of diagnosis, with the involvement of at least 1 organ with characteristics consistent with aGVHD.

Will not be considered oGVHD:

- Patients with only signs of acute GVHD (either classic or late acute)
- Patients with only signs of chronic GVHD (either classic or early) or progressive cGVHD

Overlap GVHD: Diagnosis Proposal

Single organs manifestations suggestive for oGVHD:

- GI: acute manifestations, such as anorexia, nausea, vomiting, diarrhea, severe abdominal pain, GI bleeding, and/or ileus

- Liver: prevalent or isolated bilirubin elevation without significant elevation of ALT

- Skin: isolated or prevalent erythema, maculopapular rash without any sclerotic/pigmentation change or nail/body hair involvement

- Mouth: isolated or prevalent gingivitis, mucositis, erythema without lichen-planus change

- Eyes: conjunctival signs such as hyperemia, ulcerative/hemorrhagic changes, pseudomembranous changes w/o cicatricial changes or corneal manifestations

Overlap GVHD: real world incidence
Criteria for accrual

Inclusion criteria

- Any age
- Any type of donor, graft source, conditioning regimen and GVHD prophylaxis
- All patients who develop oGVHD after allogeneic transplantation. Overalp GVHD will be defined as follow:
  a. patients developing aGVHD associated with at least 1 organ with diagnostic/distinctive features of cGVHD within 30 days from diagnosis,
  b. patients developing cGVHD associated, within 30 days of diagnosis, with the involvement of at least 1 organ with characteristics compatible with aGVHD (diarrhea or/and nausea not solely explained by other causes), isolated hyperbilirubinemia without significant ALT elevation (<3x UPN), erythema lacking distinctive or diagnostic signs of cGVHD).
  c. progressive chronic GVHD is a criterion of exclusion of diagnosis of oGVHD
- All patients with cGVHD, either classic or early, will be included as comparators
- Written and signed study informed consent

Exclusion criteria

- Absence of informed consents
- Patients developing oGVHD after 2nd allogeneic transplantation
- Patients with diagnosis of only aGVHD, either classic or late acute

Overlap GVHD: real world incidence
Endpoint 1 Method

In order to capture the real word incidence of oGVHD, we propose to:

1) Use a prototype of software developed by the center of Ancona Transplant Center for the management of patients with cGVHD. This software has been integrated with algorithms that automatically determine severity of cGVHD and overall response according to the 2015 NIH consensus criteria. This software was employed in the GITMO GVCrOSy study.

2) The software has been modified to include the signs of aGVHD and to automatically recognize oGVHD

3) A **redcap platform** has been generated in order to facilitate data collection from the GITMO centers. All participating centers will have to record all patients with chronic GVHD or overlap chronic GVHD in order to identify the real proportion of patients with overlap syndrome

Overlap GVHD: real world incidence
Endpoint 1 Method

Data to be recorded on the platform for pts with oGVHD:

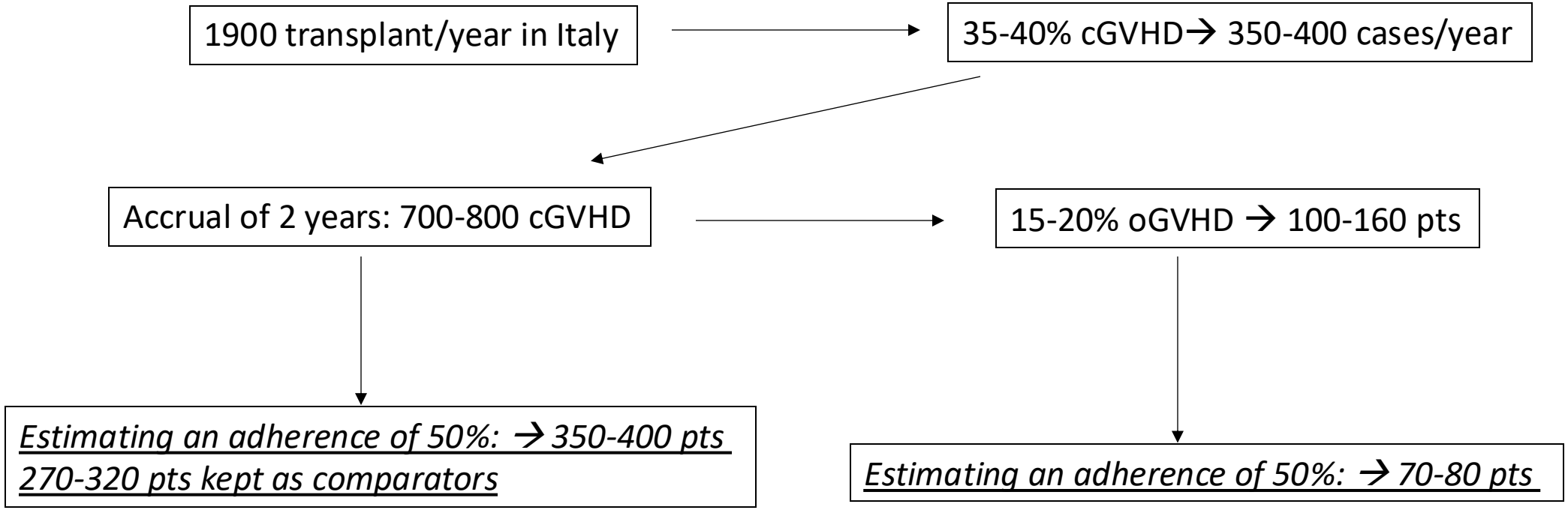
- Clinical signs of acute and chronic GVHD (see NIH consensus 2006-2015)

- Staging system used by the center (acute: MAGIC criteria, chronic: 2015 NIH criteria)

- Patients and donor characteristics, transplant characteristics, GVHD prophylaxis (see GVHD Dictionary by COST)

Overlap GVHD: population to study

Preliminary Statistical plan: Since the real word incidence of oGVHD is not known, it is not possible to plan head the alpha and beta-power of the test



- **Accrual:** 2 and half years
- **Follow-up**: 1 year after the last patient accrual

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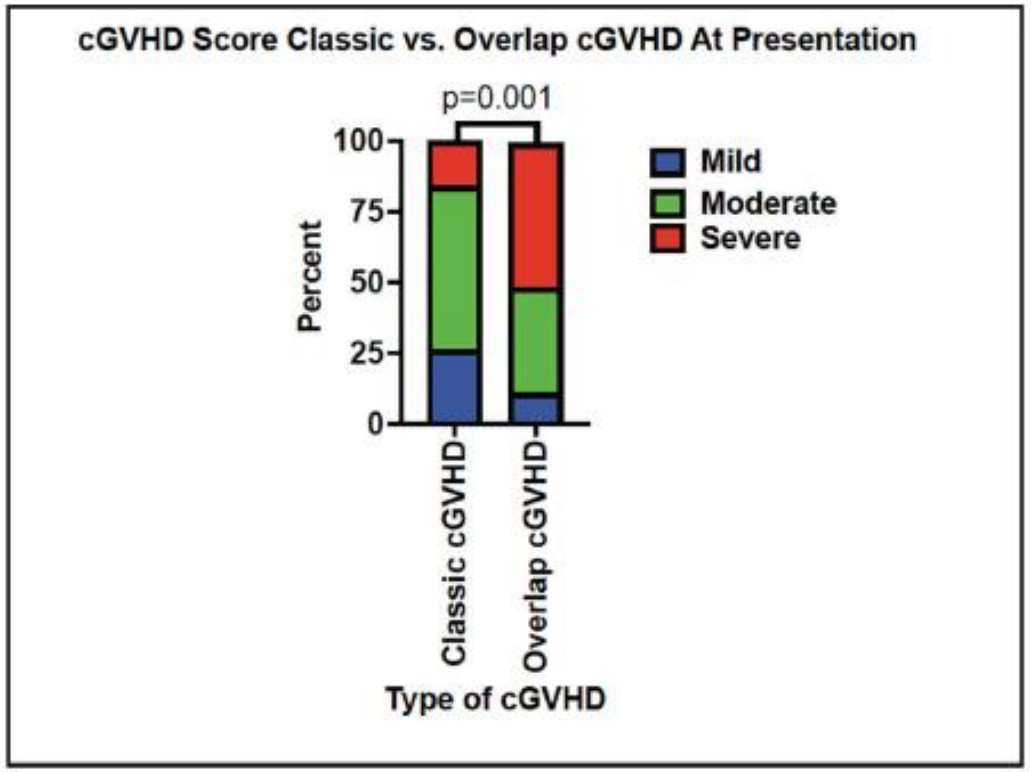
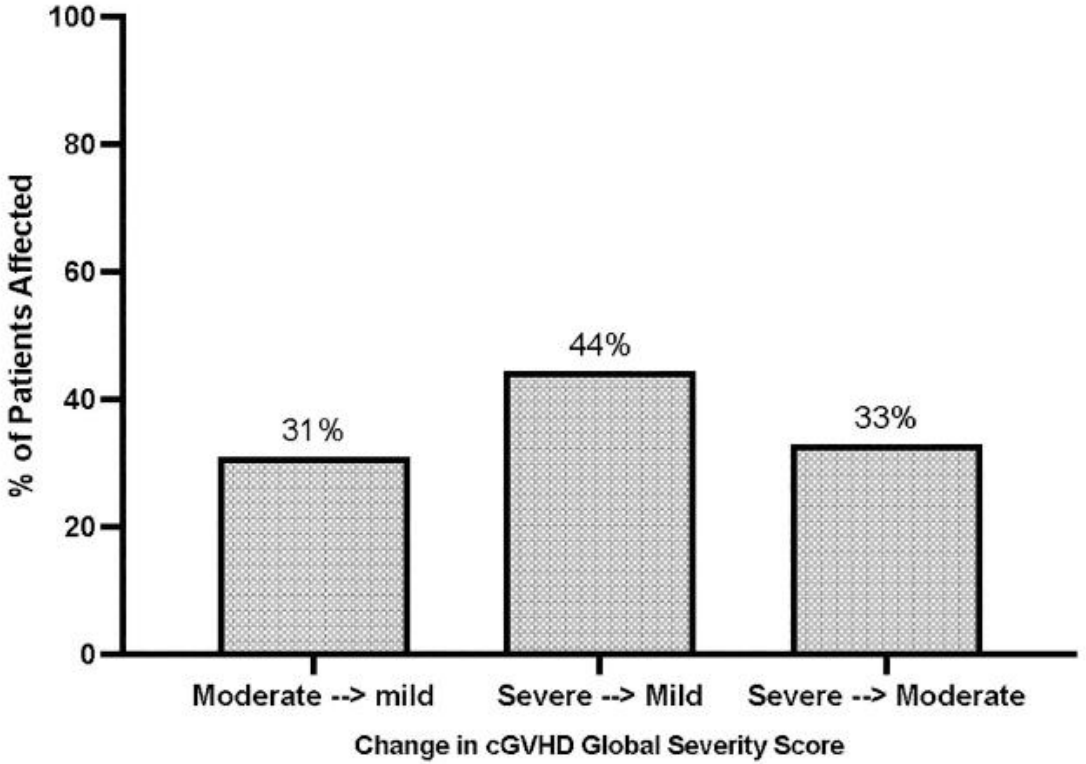
Secondary Objective

The secondary objective is to characterize the outcome and clinical response to available treatments for patients developing oGVHD and compare them with those of patients with chronic GVHD

Overlap GVHD: background
cGVHD change of stage with aGVHD features

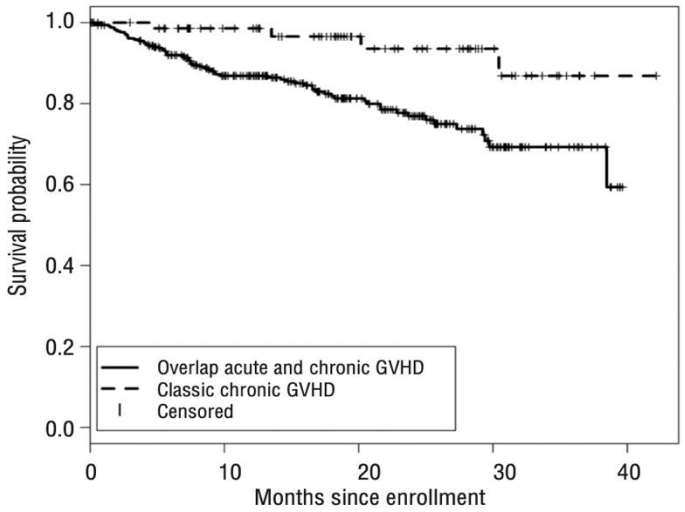


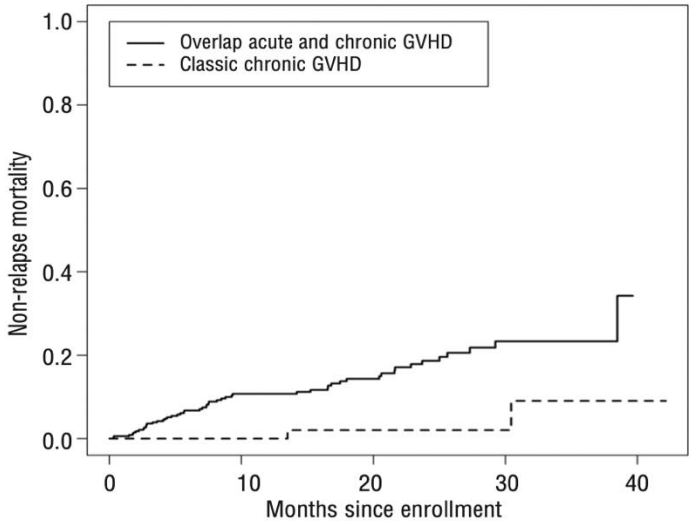


Gorfinkel L et al, BBMT 2024

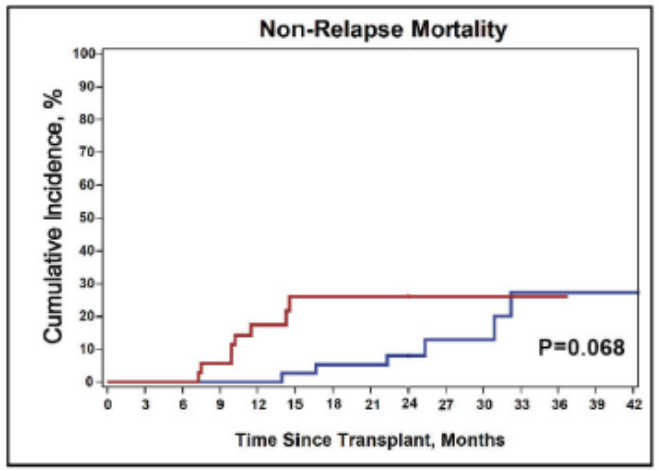
Overlap GVHD- secondary objectives

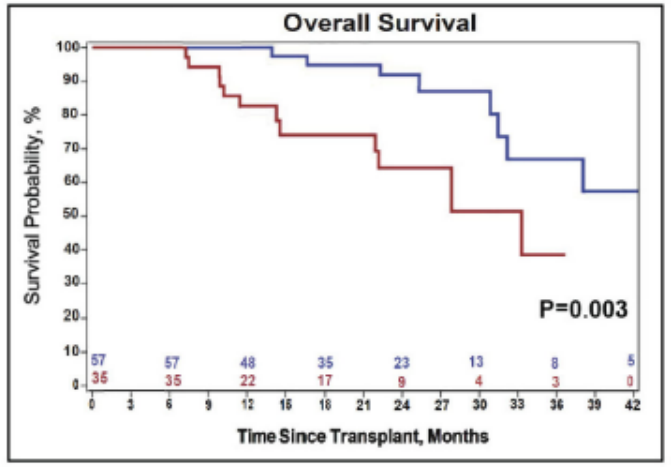
Background





Pidala J at al, Haematologica 2012





Gorfinkel L at al, BMT 2024

Langer R et al, BMT 2024,: 4,8 higher chance of death for oGVHD

Overlap GVHD- secondary objectives

- Identify and describe the most common clinical patterns of oGVHD
- Identify the most common treatments used at the GITMO centers
- Global and organ-specific response rate (RR) according to MAGIC or NIH 2015 criteria, evaluated at 1, 3 and 12 months after starting systemic treatment
- Cumulative incidence of: (1) relapse of underlying haematological malignancy; (2) non-relapse mortality (NRM), defined as any death not due to disease relapse or progression; (3) treatment change, measured from start of first and subsequent lines of treatment
- Cumulative incidence of successful withdrawal of immunosuppressive treatment, measured from start of first and subsequent lines of treatment
- Overall Survival, defined as the probability of overall survival, measured from oGVHD diagnosis
- Incidence of Severe Adverse Events (SAE), toxicities (according to the Common Terminology Criteria for Adverse Events – CTCAE), infections during treatments.- Compare the outcome of the subsets of patients with cGVHD and oGVHD
- Compare the outcome of the subsets of patients with cGVHD and oGVHD

Overlap GVHD-Ancillary Enpoint

Identify whether oGVHD is characterized by a distinctive immunologic signature

Method

Analysis at 3 different time points (0, 1 month, 3 months) of:

- Viable cells: T, B, NK, ILC compartment (immunophenotype, gene expression profile and functional activity) by using CyTOF workflow
- Cytokine profile such as ST2, RAG3-alpha, BAFF, IL-2, IFN-gamma, IL-6, PTX3, IL-12, TNF-alpha, etc…
- circulating microvescicles
- Potential extension of this analysis: collect blood and stool samples from all patients (chronic/overlap) in order to identify immunological signatures that may distinguish oGVHD from cGVHD

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