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ORIGINAL ARTICLE

Favourable survival in "Discordant" acute gastrointestinal graft versus host disease (GI-GVHD) is explained by mild clinical course and treatment-responsive disease

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Abstract

We have previously reported that haematopoietic progenitor cell transplantation recipients with biopsy-negative acute Gastrointestinal Graft versus Host Disease (Discordant GVHD) demonstrate superior survival compared to "True Positive" cases. We aimed to elucidate this discrepancy by examining clinical and laboratory predictors of survival among patients treated for True Positive or Discordant GVHD. Data were obtained by retrospective chart review. At diagnosis, the incidence of severe symptoms, hypoalbuminaemia, hyperbilirubinaemia, and poor performance status were recorded. Following treatment, the incidence of non-response to first-line corticosteroids was assessed. Differences between cohorts were compared using Fisher's exact test. 74 patients were identified, comprising 55 (74%) True Positive and 19 (26%) Discordant GVHD cases. True Positive cases were significantly more likely to have baseline severe symptoms (84% vs. 36%; $p=0.0002$) and hypoalbuminaemia (94% vs. 75%; $p=0.023$). There was no significant difference between cohorts in terms of hyperbilirubinaemia or performance status. Non-response to corticosteroid therapy was observed significantly more frequently in the True Positive cohort (55% vs. 11%; $p=0.001$). In summary, the superior survival observed in Discordant GVHD is explained by a less severe GI-GVHD phenotype at diagnosis and a greater likelihood of response to corticosteroids. Further research is warranted to explain biological mechanisms for these findings.

Keywords GVHD · HSCT · BMT

Introduction

Acute gastrointestinal graft versus host disease (GI-GVHD) is a common, life-threatening complication following haematopoietic stem cell transplantation (HSCT). Preferably, GI-GVHD is diagnosed based on histological examination of gastrointestinal tract (GIT) mucosal biopsies (True Positive GVHD); however, in the absence of histological proof, a clinical diagnosis of GI-GVHD can still be made if there is a high pre-test probability of GVHD, if alternative pathologies have been excluded, and if the patient worsens or fails to improve with supportive care alone (Discordant GVHD).

We have previously reported that patients with Discordant GVHD represent up to 26% of those who are ultimately treated for GI-GVHD [1]. These patients show significantly inferior survival compared to True Negative cases (negative biopsies, not treated for GI-GVHD), but significantly superior compared to True Positive cases (positive biopsies, treated for GI-GVHD) (1-year overall survival [OS] 66%, 88% and 48% respectively) [1].

It is unclear whether the discrepant survival in Discordant cases represent a "less severe" or "more treatment-responsive" form of GI-GVHD. Clinical and laboratory markers of GVHD outcomes may help to elucidate this survival discrepancy.

Glucksberg Stage and Grade [2, 3], pre-treatment hypoalbuminaemia [4, 5], hyperbilirubinaemia [6], and poor performance status [7, 8] have each been associated with worse response rates and survival following anti-GVHD therapy. Furthermore, a suboptimal or worsening clinical response

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following standard first-line corticosteroid treatment for GI-GVHD is associated with inferior survival [7].

We aimed to examine whether assessment of these clinical and laboratory markers aids explanation of the survival discrepancy between Discordant GVHD and True Positive GVHD cohorts.

Materials and methods

Population details

We performed a retrospective audit of HSCT recipients at our institution who had undergone investigation and treatment for acute GI-GVHD between January 2011 and December 2016.

GI-GVHD was defined by the following clinical and laboratory criteria, occurring within the same clinical episode of care:

- Patients must have new-onset significant volume diarrhoea (> 500 mL per day), ± abdominal pain, bleeding or ileus, occurring following neutrophil engraftment but prior to D + 180 following allogeneic HSCT;
- Patients must have required hospitalisation for investigation and treatment of their symptoms;
- Patients must have undergone diagnostic lower ± upper endoscopy for suspected GVHD, and for the exclusion of alternative diagnoses. Histological proof of acute GVHD was not required if no alternative pathology was identified, and if all remaining criteria were also met;
- Infectious gastroenteritis (including but not limited to: *Clostridium difficile*, rotavirus, and other bacterial, viral and protozoal infestations) must have been excluded by serial stool examination using microscopy, culture and polymerase chain reaction (PCR) assays;
- Cytomegalovirus (CMV) reactivation (defined by detectable CMV DNA levels of > 600 copies at the time of presentation, or histologically proven CMV inclusions on endoscopic biopsy) must also have been excluded;
- Patient symptoms must have worsened or failed to improve with supportive care alone;
- Patients must have ultimately been treated with methylprednisone 2 mg/kg/day as anti-GVHD treatment for their diarrhoea. Patients who did not receive this were excluded;
- Cases of isolated upper GI-GVHD (without concomitant lower GI-GVHD) were excluded.

Of these patients with GI-GVHD, all were retrospectively classified into one of the following cohorts:

- True Positive: if definitive histological GVHD was identified on endoscopy;
- Discordant: if no definitive histological GVHD was identified on endoscopy, but no competing alternative diagnosis could be identified.

Clinical and laboratory data pertaining to these two cohorts were obtained by retrospective chart review. Firstly, we recorded the incidence of severe (Grade III–IV) GI-GVHD at the time of initiating anti-GVHD therapy. Secondly, we assessed the incidence of the following pre-treatment predictors of response to anti-GVHD therapy: serum albumin ≤ 34 g/L, serum bilirubin ≥ 51 μmol/L, and poor performance status (ECOG [Eastern Co-operative Oncology Group] score ≥ 3). Thirdly, we reviewed the GIT histology obtained from endoscopic biopsy at the time of diagnosis. Finally, we assessed the incidence of non-response to therapy, which was defined by progressive disease or less than partial response within 14 days of commencement of first-line anti-GVHD therapy.

Definitions

GVHD Grade was defined as per the modified Glucksberg criteria [2], and GVHD response was defined using standard criteria [9]. Anti-GVHD therapy was defined by the commencement of corticosteroids using a minimum of methylprednisone 2 mg/kg/day. Histological GVHD was reported using established criteria in terms of apoptosis, crypt loss, inflammation, and crypt abscesses; CMV inclusions, organisms and malignancies were reported if identified.

HSCT details

All patients underwent T cell replete HSCT or donor lymphocyte reinfusion (DLI), from either matched sibling or volunteer unrelated allogeneic donors, for the treatment of haematological malignancy. Myeloablative conditioning (MAC) regimens included cyclophosphamide 60 mg/kg/day D-5 and D-4, *plus* total body irradiation 2 Gy bd D-3 to D-1 (Cy/TBI). Reduced intensity conditioning (RIC) regimens included: fludarabine 25 mg/m^2 D-7 to D-3 *plus* melphalan 120 mg/m^2 D-2 (Flu-Mel). Non-myeloablative conditioning (NMAC) regimens included fludarabine 25 mg/m^2 D-8 to D-4 *plus* cyclophosphamide 60 mg/kg/day D-3 and D-2 (Flu-Cy) and fludarabine 30 mg/m^2 D-4 to D-2 *plus* total body irradiation 2 Gy D-1 (Flu-TBI). GVHD prophylaxis for MAC and RIC transplants consisted of intravenous cyclosporine A (CsA), *plus* D + 1, + 3, + 6 and + 11 methotrexate. GVHD prophylaxis for NMAC transplants included oral CsA *plus* mycophenolate mofetil (MMF).

Statistical analysis

Fisher's exact test was used for assessment of 2 × 2 contingency tables for categorical variables, using Prism 7 (GraphPad, CA, USA).

Results

Of the 551 HSCT procedures performed during the evaluable period, 123 patients underwent endoscopy for suspected GI-GVHD. Of these, 76 received treatment for a final clinical diagnosis of GI-GVHD. Two patients were excluded due to insufficient available data, leaving 74 cases available for analysis. Of these, 55 (74%) were classified as True Positive GVHD and 19 (26%) were classified as Discordant GVHD. Details are summarised in Table 1.

Pre-treatment GVHD severity and predictors of response are described in Table 2. Notably, patients with True Positive GVHD were significantly more likely to have baseline severe symptoms and hypoalbuminaemia compared to patients with Discordant GVHD. Baseline bilirubin and performance status did not significantly differ between cohorts.

On endoscopy, macroscopic GVHD was reported in 37 (67%) True Positive patients and 5 (26%) Discordant patients.

Review of GIT histology revealed GVHD in 100% of True Positive cases and 0% of Discordant cases. All Discordant cases demonstrated normal GIT histology, without any inflammation, apoptosis, crypt dropout or malignancy.

Following commencement of first-line anti-GVHD therapy, non-response was observed significantly more frequently in the True Positive cohort (30 patients, 55%) compared to the Discordant cohort (2 patients, 11%; $p = 0.001$).

Discussion

We have previously reported that patients with Discordant GVHD have survival outcomes superior to patients with True Positive GVHD. In this follow-up study, we report that the superior survival observed in patients with Discordant GVHD appears to be explained by a less severe GI-GVHD phenotype at diagnosis, and a higher likelihood of response to first-line corticosteroid therapy for GVHD.

Why Discordant patients have a less severe clinical phenotype is not clear. Although spurious "over-diagnosis" of GI-GVHD at our centre is possible, we contend that our definition for GI-GVHD is sufficiently robust to preclude this. Although it is possible that the negative biopsies in Discordant cases may represent sampling error during endoscopy, sampling error does not fully explain the differing clinical phenotype and survival outcomes.

A lack of histologically abnormal GIT tissue may reflect less extensive GIT involvement by GI-GVHD, or involvement by less secretory anatomical GIT regions that are not easily reached by endoscopy. In cases of fulminant severe GI-GVHD, the GIT mucosa can become irrevocably damaged by full thickness ulceration with little prospect of recovery [7, 10, 11]; the relatively low frequency of these cases among the Discordant cohort may reflect a biologically more "mild" form of the disease.

These hypotheses may be further explored using novel techniques, which hitherto have been developed for predicting the onset or severity of GI-GVHD. Measurement of plasma biomarkers for GVHD, including angiogenic factors and cytokines such as ST2, IL2Ra and TNFR1 [12–15], could be compared between True Positive and Discordant cohorts to examine any potential biological differences between these GI-GVHD phenotypes. Intestinal imaging using positron emission tomography (PET) [16–19] or ultrasound [20] could be employed to compare differences in anatomical distribution of GI-GVHD between cohorts.

Recognition of differing GI-GVHD phenotypes and their underlying biology may inform subsequent optimisation of GVHD treatment strategies. Given the significant difference in steroid-responsiveness between cohorts, True Positive cases may warrant early escalation to second-line anti-GVHD therapy or novel agents, while Discordant cases appear to usually respond to steroids alone. Accurate detection, diagnosis and prognostication of GI-GVHD will allow for more robust clinical trial design to answer these management questions.

The main limitation of our study is its retrospective design, which is not dissimilar to other reports in the literature.

Conclusion

The superior survival observed in patients with Discordant GVHD, compared to True Positive GI-GVHD, appears to be explained by a less severe clinical GVHD phenotype at diagnosis and a higher likelihood of response to first-line corticosteroid treatment. Further research is warranted to explain biological mechanisms for these findings, and to develop diagnostic techniques that better identify differing GI-GVHD phenotypes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

See Tables 1 and 2.

Table 1 Baseline characteristics of HSCT recipients upon commencing treatment for GI-GVHD

Characteristic	Number (%)
Number	74
Median age (years)	53 (range 17–69 years)
Male gender	52 (70%)
Pre-HSCT haematological diagnosis	
AML	23 (31%)
ALL	16 (22%)
MDS/MPN	22 (30%)
LPD	13 (17%)
HSCT conditioning regimen	
Myeloablative	25 (34%)
Reduced intensity	44 (59%)
Non-myeloablative	5 (7%)
HPC donor	
Matched sibling	17 (23%)
Matched unrelated donor	57 (77%)
Sex matched	17 (23%)
ABO matched	19 (26%)
CMV matched	42 (57%)
PBSC as HPC source	74 (100%)
GI-GVHD classification	
True positive GVHD	55 (74%)
Discordant GVHD	19 (26%)

AML acute myeloid leukaemia, *ALL* acute lymphoblastic leukaemia, *MDS/MPN* myelodysplastic syndromes and myeloproliferative neoplasms, *LPD* lymphoproliferative disease, *CMV* cytomegalovirus, *PBSC* peripheral blood stem cells, *HPC* haematopoietic progenitor cell, *HSCT* haematopoietic stem cell transplant, *GVHD* graft versus host disease

Table 2 Pre-treatment predictors of response to first-line corticosteroid therapy in patients with True Positive versus Discordant GVHD

	True positive cohort	Discordant cohort	*p* value
Number	55	19	
Symptom severity			
Median stage	2 (1–4)	1 (1–4)	0.0002
Maximum grade	3 (1–4)	2 (–4)	
Grade III–IV	46 (84%)	7 (36%)	
Serum albumin ≤ 34 g/L	53 (96%)	16 (74%)	0.023
Serum bilirubin ≥ 51 µmol/L	2 (4%)	0 (0%)	1.0
ECOG ≥ 3	12 (22%)	4 (21%)	1.0

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