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Granulocyte Macrophage Colony Stimulating Factor Treatment is Associated with Improved Cognition in Cancer Patients

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Abstract

Background: Endogenous Granulocyte Macrophage Colony Stimulating Factor (GMCSF) is released in rheumatoid arthritis patients, who are largely protected from Alzheimer's disease (AD). Introducing exogenous GMCSF into an AD mouse model reduced amyloid deposition by 55% and restored normal cognition. No published studies have examined exogenous GMCSF and cognitive functioning in humans.

Objectives/ Design: The goal of the current study was to examine the association between receipt of GMCSF and cognitive functioning in patients receiving colony stimulating factors as part of routine supportive care for hematopoietic cell transplantation (HCT).

Setting and Participants: Archived neuropsychological data were examined from a longitudinal study of cognitive functioning in 95 patients receiving HCT at the Moffitt Cancer Center.

Intervention: Receipt of GMCSF and/or Granulocyte Colony Stimulating Factor (GCSF) was ascertained through patient billing records.

Measurements: Patients were assessed with a battery of neuropsychological tests prior to transplant and 6 and 12 months post-transplant.

Results: Patients treated with GMCSF and GCSF (n=19) showed significantly greater improvement in total neuropsychological functioning (TNP) at 6 months than patients treated with GCSF only (n=76) (p=.04). There was no group difference in TNP at 12 months (p=.24). Improvement in TNP from baseline to 6 months post-HCT was significant in the GMCSF+GCSF group (p=.01) but not the GCSF only group (p=.33). Improvement in TNP from baseline to 12 months post-HCT was significant in both groups (ps<.01).

Conclusion: Preliminary data from this study of humans receiving colony stimulating factors suggest that receipt of GMCSF+GCSF was associated with greater cognitive improvement than GCSF alone. Randomized controlled trials of the effects of GMCSF on cognitive functioning in humans are warranted and underway to confirm these findings.

Keywords: Neoplasms; Alzheimer's disease; Autoimmune diseases; Granulocyte-macrophage colony-stimulating factor; Neurobehavioral manifestations; Hematopoietic cell transplantation

Introduction

Cognitive decline is a major societal concern due to the aging population of many industrialized nations. Cognitive decline not only results from the aging process itself, but also neurodegenerative diseases such as Alzheimer's disease (AD) and some treatments for other common age-related diseases, such as cancer [1-3]. Thus far, no effective pharmacologic treatment that reverses cognitive decline has been developed for any indication.

One potentially promising treatment is granulocyte macrophage colony stimulating factor (GMCSF). Clinical interest in GMCSF developed out of the observation that patients with Rheumatoid Arthritis (RA) are at 8-fold reduced risk of developing AD. This finding was originally hypothesized to result from patients' use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) [4]. Although early findings showed inflammation proteins playing an essential role in AD [5], NSAIDs trials in AD were largely negative [6]. Instead, endogenous factors, specifically several colony stimulating factors (CSFs) released during RA, might activate the innate immune system and thereby also reduce pathology and promote neurogenesis and angiogenesis in the AD brain [7].

Experimental research in mice has found that a single injection of GMCSF or granulocyte colony stimulating factor (GCSF) into one side of the brain reduced amyloid deposition by up to 40% in 7 days compared to the vehicle injected side, with GMCSF being more efficacious than GCSF [7,8]. These findings were confirmed by additional experiments examining neuronal and behavioral outcomes after sub-cutaneous administration of GMCSF or GCSF [7,8]. Compared to GCSF, GMCSF exhibited greater impact on cognition, which returned to normal. These findings, along with two decades of excellent safety data from the administration of recombinant human GMCSF (sargramostim) to elderly leukopenic patients suggests that CSFs, particularly GMCSF, should be tested in randomized controlled trials as a treatment to halt or reverse cognitive impairment in humans [7].

The aim of the present study was to provide preliminary

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observational data in support of such trials. Because CSFs are routinely administered to cancer patients undergoing autologous HCT, and HCT is associated with transient cognitive decline [9,10], this population provides an ideal opportunity to study cognitive functioning related to receipt of GMCSF. It was hypothesized that HCT patients treated with GMCSF would display greater increases in cognitive functioning over time compared to patients treated with GCSF.

Methods and Materials

We examined archived neuropsychological data from a longitudinal study of the cognitive function of patients at Moffitt Cancer Center [11]. GMCSF and GCSF are used as part of routine supportive care to mobilize stem cells for autologous HCT, speed engraftment after autologous HCT, and/or treat neutropenia following allogeneic HCT. Choice of GMCSF+GCSF versus GCSF alone was based solely on availability and/or reimbursement options and was not related to clinical or sociodemographic factors or desire of the patient.

Following Institutional Review Board approval, patients were recruited between February 2001 and September 2004. To be eligible for the larger study, patients had to: 1) be between 18 and 75 years of age, 2) have completed at least 8 years of education, 3) be able to speak and read English, 4) be scheduled to receive HCT, 5) plan to return to Moffitt for follow-up assessments, and 6) be able to provide informed consent. Prior to stem cell mobilization and HCT, patients completed a baseline neuropsychological assessment and provided sociodemographic information [11]. Follow-up neuropsychological assessments were conducted at 6 months and 12 months post-HCT. Neuropsychological tests are listed in (Table 1). Patients who completed a baseline neuropsychological assessment and at least one follow-up assessment were selected for the current analyses. Patients who received all administrations of GMCSF and/or GCSF at a location other than Moffitt were excluded from the analyses.

Data regarding receipt of GMCSF (i.e., sargramostim) and/or GCSF (i.e, filgrastim, pegfilgrastim) were collected via patient billing records. For the current analyses, total neuropsychological performance z scores (TNP) were calculated by summarizing the cognitive domains of memory, executive functioning (i.e., complex cognition), and attention. Scores indicate change in TNP from pre-transplant baseline. Kruskal-Wallis one-way analyses of variance were conducted using all available data to compare between-group changes in TNP by receipt of GMCSF at Times 2 and 3. Wilcoxon signed rank tests were conducted using all available data to examine within-group changes in TNP by receipt of GMCSF.

Cognitive domain	Neuropsychological Tests
Memory	CVLT-II [26]
	WMS-III Logical Memory subtest [27]
	WMS-III Visual Reproduction subtest [27]
Executive function	WAIS-R Digit Symbol [28]
	Trailmaking Test [29]
	COWA [30]
	Stroop Neuropsychological Screening Test [31]
Attention	CPT –II [32]

Note: COWA: Controlled Oral Word Association Test, CPT-II: Connors' Continuous Performance Test – II, CVLT-II: California Verbal Learning Test – II, WAIS-R: Wechsler Adult Intelligence Scale – Revised, WMS-III: Wechsler Memory Test - III.

Table 1: Neuropsychological Tests Administered.

Results

Of 286 participants who signed consent and completed a baseline assessment, 182 had no follow-up data, 4 had received GMCSF and/or GCSF elsewhere, and 5 had not received GMCSF or GCSF, leaving a final sample of 95 participants. Of these, 89 participants had baseline and 6 month follow-up data, 63 had baseline and 12 month data, and 57 had data at all 3 assessment points. A total of 19 patients received GMCSF+GCSF, and 76 received GCSF only. No patients received GMCSF only. Patients had a mean age of 51 (range 21-72), 48% were female, 83% were Caucasian, and 32% had graduated from college. Most patients were diagnosed with multiple myeloma or non-Hodgkin's lymphoma (78%) and received autologous HCT (83%) (Table 2).

Despite a high level of education (average of 13.89 years), participants displayed a statistically significant cognitive deficit at baseline [11]. The results (Figure 1) show that the GMCSF+GCSF group performed significantly better than the GCSF only group at 6 months post-HCT (p=.04), but there were no group difference at 12 months post-HCT (p=.24). Change in TNP from baseline to 6 months post-HCT was significant in the GMCSF+GCSF group (p=.01) but not

	GMCSF+GCSF (n=19)	GCSF Only (n=76)	*p*
Age: Mean (SD)	58.06 (8.22)	50.41 (11.90)	.01
Years of Education: Mean (SD)	14.11 (2.56)	14.00 (2.96)	.59
Estimated Premorbid IQ: Mean (SD)	105.05 (9.22)	105.80 (11.22)	.69
Baseline Functional Status ECOG	1.32 (.89)	1.05 (.80)	.27
Gender			.44
	Female	11 (58%)	35 (46%)
	Male	8 (42%)	41 (54%)
Race			.73
	Caucasian	15 (79%)	64 (84%)
	Non-Caucasian	4 (21%)	12 (16%)
Diagnosis			.09
	Multiple Myeloma	17 (89%)	51 (67%)
	Acute Myelogenous Leukemia	1 (5%)	3 (4%)
	Myelodysplastic Syndrome	0 (0%)	2 (3%)
	Acute Lymphoblastic Leukemia	0 (0%)	1 (1%)
	Breast Carcinoma	1 (5%)	5 (7%)
	Chronic Lymphocytic Leukemia	0 (0%)	1 (1%)
	Chronic Myelogenous Leukemia	0 (0%)	2 (3%)
	Myeloproliferative neoplasm	0 (0%)	1 (1%)
	Hodgkin's Lymphoma	0 (0%)	2 (3%)
	Non Hodgkin's Lymphoma	0 (0%)	6 (8%)
	Aplastic Anemia	0 (0%)	2 (3%)
Transplant type			.18
	Autologous	18 (95%)	61 (80%)
	Allogeneic	1 (5%)	15 (20%)

Note: Kruskal-Wallace one way analyses of variance were used to compare GMCSF+GCSF, and GCSF only groups on age, years of education, estimated premorbid IQ, and ECOG. Fisher's exact tests were used to compare GMCSF+GCSF and GCSF only groups on gender, race, diagnosis, and transplant type. Diagnosis was coded as Multiple Myeloma versus other.

Table 2: Categories of gender, race, diagnosis, transplant type need to be moved to the left in a new column so that the numbers correspond to the column headings of GMCSF+GCSF and GCSF only.

	GMCSF+GCSF		GCSF Only	
	6 Months	12 Months	6 Months	12 Months
TNP	.19 (.27)	.34 (.43)	.03 (.30)	.24 (.33)
Memory	.45 (.54)	.48 (.63)	.11 (.53)	.40 (.49)
Executive Function	.23 (.59)	.53 (.72)	.12 (.62)	.37 (.64)
Attention	-.10 (.46)	.02 (.40)	-.13 (.49)	-.04 (.49)

Note: unit of change is standard deviations. HCT: Hematopoietic cell transplant, TNP: total neuropsychological performance

Table 3: Changes in Cognitive Domains from Baseline to 6 and 12 Months Post-HCT.

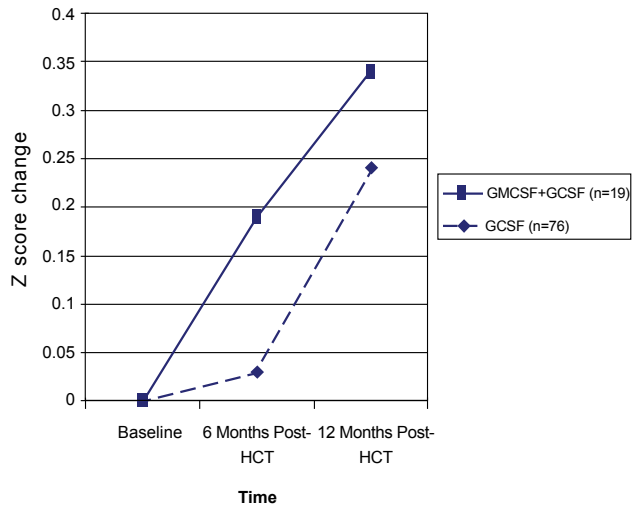

Figure 1: Total Neuropsychological Performance in Hematopoietic Cell Transplant Recipients Receiving GMCSF+GCSF versus GCSF only. The GMCSF+GCSF group performed significantly better at 6 months post-HCT (p=.04), but there were no group differences at 12 months post-HCT (p=.24). The GMCSF+GCSF group improved significantly from baseline to 6 months post-HCT (p=.01) and from baseline to 12 months post-HCT (p<.01). The GCSF group demonstrated no change from baseline to 6 months post-HCT (p=.33) but significant improvement from baseline to 12 months post-HCT (p<.01).

in the GCSF only group (p=.33). Change in TNP from baseline to 12 months post-HCT was significant in both groups (ps<.01). The TNP results were mainly driven by the memory domain; at 6 months, the GMCSF group performed significantly better than the GCSF only group on memory (p=.04), but there were no group differences in attention and executive function (ps>.48). At 12 months, there were no group differences in any domain (ps>.26). From baseline to 6 months, the GMSCF group improved in memory (p<.01) while the GCSF group did not improve in any domain (ps>.07). From baseline to 12 months, both groups improved in memory and executive function (ps≤.01).

Discussion

The current study examined observational data regarding the relationship between receipt of CSFs and cognition in humans. Findings indicate that receipt of both GMCSF+GCSF was associated with improved cognition in cancer patients receiving HCT, with the inclusion of GMCSF being associated with greater cognitive improvement than GCSF alone. The improvement in cognition was strongest in the memory domain at 6 months and extended to the executive domain by 12 months.

Because study participants were not randomly assigned to receive GMCSF+GCSF versus GCSF alone, and information on cognition of patients with the same diagnosis and who received neither CSF were not available, the results cannot be interpreted as showing a cause-effect relationship between receipt of CSF and cognitive improvement. Nevertheless, because the choice of CSF was based on considerations independent of the disease status of the patient, there is unlikely to be a consistent bias in drug choice that could explain the observed differences in cognitive outcome in patients receiving both GMCSF+GCSF vs GCSF alone. Because the sample size was small, we also cannot rule out the possibility that results are due to sample variability. However, the positive findings in the current study combined with the experimental demonstration that CSFs improve cognition in animals argue for additional research examining CSFs on cognition in humans. This research should consist of well-powered randomized clinical trials to examine the causal effects of GMCSF on cognition in clinical populations. A pilot trial is underway to assess the safety and efficacy of GM-CSF in the treatment of Alzheimer's disease.

The mechanism by which GMCSF and GCSF reverse cognitive deficits in mouse models of AD, and possibly protect RA patients from AD, may be due to reducing amyloid deposition or stimulating angiogenesis, neurite outgrowth, and/or neuronal survival [7,8]. Amyloid reduction could result from induced phagocytosis by activated microglia/infiltrating macrophages and neutrophils [7,8,12,13], with macrophages having greater phagocytic ability [14], by induction of MMP-9 from infiltrating macrophages/neutrophils [15-17], by reduced deposition, or by a combination of these mechanisms. In as much as the inflammatory proteins α1-antichymotrypsin and/or apolipoprotein E are essential for efficient amyloid formation in vitro and in vivo [5,18,19], it is interesting that GMCSF reduces macrophages and/or microglia production of apoE by 3.5 fold, and of the ACT and apoE-inducing cytokine Il-1 by 2 fold [20,21], and that cancer patients also over-express IL-1 and IL-6 [22,23]. However, because amyloid deposition in normal subjects arises late in life, the effect of CSF treatment in these cancer patients may be more related to other targets of the innate immune system such as cell debris or glial scar or may arise from induced angiogenesis or neurite outgrowth [7]. Because GCSF and GM-CSF are able to cross the blood brain barrier, the mechanism of cognitive improvement could include both peripheral and direct CNS activities 25-26. The finding that GMCSF + GCSF was associated with greater cognitive improvement than was GCSF alone parallels the finding in AD mice and may reflect the broader cell type recruitment induced by GMCSF, specifically in the phagocytic monocyte microglial lineage [7,8].

In sum, the data presented here, although preliminary and retrospective, indicate that CSFs, particularly GMCSF, should be further tested as cognition enhancers for a number of different indications including cancer and neurodegenerative disease. The current data provided the basis for an FDA and IRB approved randomized clinical trial currently underway in human AD patients to evaluate the safety and potential effects of GMCSF on cognition. Thus far no serious adverse events have been recorded.

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University of South Florida has applied for (but not licensed) a patent on using GMCSF to treat cognitive decline, on which HP and TB are two of the four inventors.

Author Contributions

Dr. Jim had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Original HCT Study concept and design: Booth-Jones.

CSF-specific data analysis concept and design: Jim, Potter.

Acquisition of the data: Booth-Jones.

Analysis and interpretation of data: Jim, Boyd, Pidala, Potter.

Drafting of manuscript: Jim, Potter.

Critical revision of the manuscript for important intellectual content: Jim, Boyd, Booth-Jones, Pidala, Potter.

Statistical analysis: Jim.

Obtained funding: BoothJones.

Administrative, technical, or material support: Jim, Boyd, Booth-Jones, Pidala, Potter.

Study supervision: Booth-Jones.

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