Brain-Derived Neurotrophic Factor Protects Against Cognitive Toxicity in Adolescent and Young Adult Cancer Patients

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INTRODUCTION

- ***Adolescent and young adult (AYA)*** cancer patients are diagnosed at a critical stage in life (15-39 years old) characterized by major physical, emotional, cognitive, and social developments.
- Due to cancer and treatment exposures, AYAs may develop cognitive toxicity which will impact their pursuit of higher education and career progression after cancer.[1,2]
- ***Brain-derived neurotrophic factor (BDNF)*** is a key biomarker of interest for preventing cognitive toxicity among cancer patients. Its ability to mediate neurogenesis and neuroplasticity may help to combat neuronal stress and toxicity induced by anticancer therapies.
- A number of studies have reported an association between plasma BDNF and cognition among older cancer patients receiving chemotherapy, but this relationship has not been established in the AYA cancer population.[3]

RESEARCH QUESTION

- Do plasma BDNF levels relate to cognitive function among AYA cancer and non-cancer populations? *We hypothesize that higher plasma BDNF levels are associated with better cognitive function and less cognitive decline in both AYA cancer and non-cancer populations.*

METHODS

- **Study design:** Prospective cohort study conducted at the National University of Singapore, National Cancer Center Singapore and KK Women's and Children's Hospital between June 2018 and June 2022. The study protocol received ethics approval from SingHealth Institutional Review Board (CIRB 2017/3139).
- **Participants:** Two groups of participants were recruited for the study. AYA cancer patients (AYAC) and age-matched non-cancer community controls (NC).
- **Study timepoints:** AYAC performed the study procedures at baseline (T1), approximately 3 (T2), and 6 (T3) months after baseline. NC will be followed up at baseline (T1) and approximately 6 (T3) months after baseline (Figure 1).

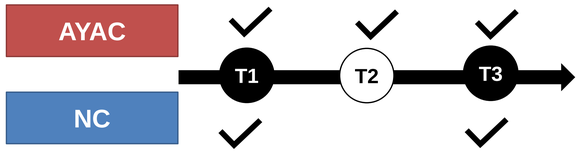


Figure 1: Study timepoints, denoting as T1, T2 and T3 for baseline, approximately 3 and 6 months after baseline, respectively.

- **Procedures:** The following study procedures were conducted at each timepoint (T1, T2, T3).
  1. Self-reported assessment of cognitive function ***(FACT-Cog)***, psychological distress ***(Rotterdam Symptom Checklist)*** and fatigue ***(Multidimensional Fatigue Symptom Inventory—Short Form)***;
  2. Neuropsychological testing with ***CANTAB®***;
  3. Blood draws for plasma collection (1,000 *x g* for 10 minutes), stored at negative 80°C until ***BDNF*** quantification using a commercially available ELISA kit (Biosensis BEK-2211-1P/2P, Australia).

RESULTS

(A) Participant characteristics

- AYAC were mostly diagnosed with breast (24%) and head/neck (22%) cancers, and receiving platinum agents (61%), anthracyclines (26%), and (24%) taxanes. Approximately half (49%) received concomitant radiotherapy and chemotherapy.

Characteristics	AYAC (N=74)	NC (N=118)	*P*
Age in years, median (IQR)	34 (29, 37)	32 (28, 35)	0.060
Gender, n (%)			0.995
Male	27 (36%)	43 (36%)	
Female	47 (64%)	75 (64%)	
Ethnicity, n (%)			**<0.001**
Chinese	51 (69%)	89 (75%)	
Malay	13 (18%)	2 (2%)	
Indian	4 (5%)	22 (19%)	
Others	6 (8%)	5 (4%)	
Marital status, n (%)			**0.013**
Never married	28 (38%)	68 (58%)	
Married	44 (60%)	48 (41%)	
Divorced	2 (3%)	1 (1%)	
Widowed	0 (0%)	1 (1%)	
Years of education, median (IQR)	15 (12, 17)	17 (16, 19)	**<0.001**

(B) Incidence of self-perceived and objective cognitive impairment

- A higher incidence of self-perceived cognitive impairment was found among AYAC receiving anthracyclines or taxanes. In contrast, more objective cognitive impairment was within those receiving platinum agents or radiotherapy with chemotherapy (Figure 2).

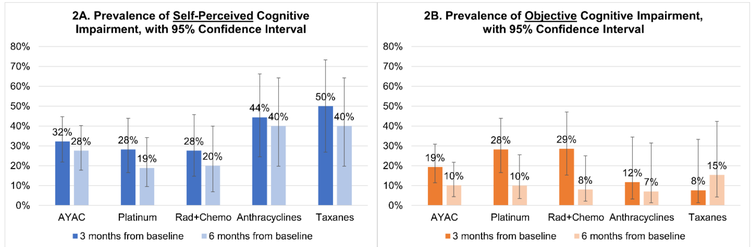
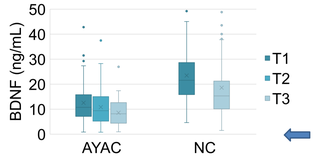


Figure 2: Longitudinal changes in (2A) self-perceived and (2B) objective cognitive outcomes.

(C) Plasma BDNF levels were lower among AYAC vs NC



- Median BDNF levels were significantly lower in AYAC compared to NC (T1: 10.7 vs 21.6, *P<0.001*; T3: 8.2 vs 15.3, *P=0.001*; Figure 3).

Figure 3: BDNF trajectories across study time points.

(D) Higher plasma BDNF levels predict better post-treatment cognitive outcomes among AYAC

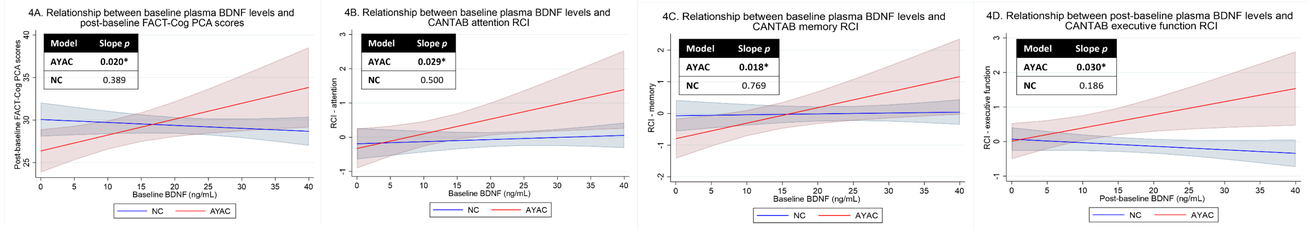


Figure 4: Relationships between plasma BDNF levels (x-axis) and post-baseline cognitive outcomes (y-axis). Higher scores represent better cognitive outcomes.

DISCUSSION

- Greater and sustained declines in self-perceived cognitive function lasting 6 months from cancer diagnosis among AYAC compared to NC corroborate with findings in past cancer studies in older adults.[4,5]
- Varying phenotypes of cognitive impairment were observed in patients with different cancer diagnosis, receiving different combinations of cytotoxic treatment and modalities. Different interventions may be required to target the different subtypes of impairment (e.g., psychosocial interventions for self-perceived cognitive impairment, and cognitive training for objective cognitive impairment).
- The positive correlation between BDNF and post-baseline cognition among AYAC provides strong evidence that higher plasma BDNF is indicative of resilience against treatment-induced neural damage through its physiological role in regulating neural growth and plasticity.
- Lower plasma BDNF levels among AYAC compared to NC was also reported in two other cancer-control comparison studies, including lung[6] and colorectal[7] cancer patients.

CONCLUSIONS

- Plasma BDNF may serve as a potential monitoring biomarker and biological target for cancer-related cognitive impairment in the AYAC population.
- Future studies can evaluate the clinical significance of raising BDNF plasma levels in cancer to a level comparable to a non-cancer individual for cognitive protection.

References

1. Brock H, et al. J Cancer Surviv. 2022 Aug;16(4):771-780.
2. Tan CJ, et al. Psychooncology. 2020 Aug;29(8):1355-1362
3. Ng DQ, et al. Crit Rev Oncol Hematol. 2022 Aug;176:103748.
4. Collins B, et al. J Int Neuropsychol Soc. 2014 Apr;20(4):370-9.
5. Vardy JL, et al. J Clin Oncol. 2015 Dec 1;33(34):4085-92.
6. Li F, et al. J Thorac Dis. 2019 Aug;11(8):3547-3555.
7. Brierley GV, et al. Cancer Biomark. 2013;13(2):67-73.

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