LETTER TO THE EDITOR

Randomizing for Alzheimer's disease drug trials should consider the cancer history of participants

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Karanth *et al*.[1] reported an inverse association between cancer diagnosis and Alzheimer's disease (AD) dementia. This study is interesting because the authors add new evidence on neuropathological changes to the existing knowledge from multiple studies that report that cancer survivors have a reduced risk of AD development. This association has been noted between most cancers and dementia due to AD but not between cancer and non-AD dementia, stroke, osteoarthritis or macular degeneration[2]. Whether this opposite effect is due to common biological and psychosocial mechanisms or pharmacological interventions remains debatable. However, retrospective analysis shows that chemotherapy may lower the risk of AD morbidity[1,2]. In colorectal cancer survivors aged > 65 years or white females aged ≥ 65 years diagnosed with breast cancer, chemotherapy use was associated with reduced AD risk[1,3]. Perimenopausal- to postmenopausal women aged 45 years or older diagnosed with breast cancer patients who received tamoxifen and exemestane were diagnosed significantly less with neurodegenerative diseases, particularly AD[4].

Extensive studies are needed to understand why cancer diagnosis or some cancer therapy reduces the risk of AD dementia. Different drugs may target different pathways, reducing neurodegeneration in AD. Further, clonal hematopoiesis, a premalignant condition, is also speculated to confer protection from AD dementia[5]. Considering that chemotherapy was administered before AD diagnosis in reported retrospective studies, we speculate that some chemotherapeutics may abrogate the formation of pathological seeds of tau or amyloid-beta (Aβ, preventing AD development. In this respect, we showed that some anticancer drugs might prevent the generation of early tau seeds that spread intraneuronally and is linked to accelerated disease progression[6]. The anticancer drugs inhibited the nucleation of tau aggregation that initiates the production of toxic oligomers, a process similar to inhibiting toxic $A\beta_{42}$ production[6].

Multiple studies are ongoing or have been completed on the efficacy of biologics and other drug types for AD treatment. Florian and colleagues recently evaluated the safety and efficacy of tilavonemab, a monoclonal anti-tau antibody, in a phase 2 study in early AD patients[7]. They reported that although the drug was well-tolerated, it did not demonstrate efficacy for AD therapy and is not expected to be investigated further. Similar studies were conducted with monoclonal antibodies against Aβ, such as gantenerumab (NCT01224106), donenemab (NCT03367403), lecanemab (NCT01767311) and aducanumab (NCT02484547 and NCT02477800). With the exception of gantenerumab, all other drugs reduced cognitive deterioration and amyloid burden in enrolled AD patients. Aducanumab and lecanemab were approved by the US Food and Drug Administration in 2021 and 2023, respectively[8,9]. Donenemab, currently in Phase 3 trial (NCT04437511), is expected to be approved in 2023 by the FDA (https://www.clinicaltrialsarena.com/news/donanemab-lecanemab/).

The tilavonemab study or trials with Aβ antibodies included a cohort of patients aged 50 to 90 who showed early AD symptoms. The inclusion criteria were based on the evidence of positive amyloid on PET or by cerebrospinal fluid testing and cognitive, functional and neuropsychological assessments. The failure of gantenerumab to meet the primary endpoint despite being a monoclonal antibody against Aβ was interesting. Perneczky *et al.*[9] explain several points, including the inclusion and exclusion criteria, that may have resulted in the negative outcome of gantenerumab compared to other trials. They highlight that the lecanemab trial had broader inclusion criteria allowing enrollment of patients with multimorbidity and ongoing treatment with other medications[9]. Some of the trials excluded patients with a history of

HIV, cardiac ailments, psychiatric disorders and neurological diseases other than AD, and of treatment with immunoglobulin G, acetylcholinesterase inhibitor or memantine, or anticoagulants; however, there is no indication on whether a history of cancer or cancer therapy was excluded.

Interestingly, one of the inclusion criteria in the gantenerumab trial was a history of radiation exposure (NCT03367403), but whether this was related to radiotherapy for cancer is unclear. Radiotherapy is associated with an increased risk of AD-related mortality in survivors of head and neck, and brain cancers[10]. Therefore, given the overwhelming link between cancer, chemotherapy and AD, clinical trials involving participants in the age range of cancer survivors should include the history of cancer and cancer therapy when interpreting the results of trials investigating biologics or other drugs for AD treatment.

Data availability

Data sharing does not apply to this article as no new data were created or analysed in the study.

Competing interests

Both authors declare no conflicts of interest/competing financial interests.

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