COMMENTARY

A New Use for an Old Treatment: Radiation Therapy and Alzheimer’s Disease

George D. Wilson and Brian Marples

Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, Michigan

ALZHEIMER’S DISEASE

Alzheimer’s disease is a neurodegenerative disorder that becomes more prevalent with increasing age. An estimated 5.2 million Americans have Alzheimer’s disease (AD), and by mid-century the number of people living with AD in the United States is projected to reach 9 million (1). It is widely acknowledged that Dr. Alois Alzheimer was the first to associate progressive cognitive impairment with the presence of senile plaques and neurofibrillary tangles in the cortex of the brain (2, 3). While Dr. Alzheimer’s initial report was presented in 1906, the cause, or causes of Alzheimer’s disease remain unclear. The complex pathology of AD, the incomplete understanding of brain dysfunction and the lack of a definitive diagnostic test have all hindered the development of clinical treatments for AD. At best, current interventions remain palliative and transient rather than disease modifying, and even fail to slow disease progression to any extent (4). The fact that basic researchers are unable to discover effective AD-specific treatments is in part due to the absence of suitable experimental models with which to study the disease. Alzheimer’s disease primarily affects cognition and cognitive function, and as such cannot be studied in cell culture, although critical elements in pathogenesis have been identified in vitro (5). Many animal models of Alzheimer’s disease (6, 7) are available, but each model investigates different aspects of AD pathology and disease progression. Consequentially, evaluating cognitive and behavioral tasks in the different transgenic mouse models, as a means of identifying an overall biological role in disease progression and AD pathophysiology, has proved challenging (8, 9).

Nevertheless, decades of research have led to the identification of key components in the pathophysiology of AD (10–12). It is now widely accepted that the chain of biochemical events thought to be responsible for AD are triggered many years prior to symptom onset. The amyloid hypothesis (10) proposes that the deposition of amyloid beta (Aβ) in brain parenchyma is an early critical event that promotes or accelerates downstream features of AD, such as tangle formation, neuronal loss and progressive dementia. Although recently reported arguments have been made supporting the relevance of continued study into Aβ modulation in the brain (13), large-scale clinical studies using antibodies against Aβ have not proven to be successful (14, 15).

The projected health care costs associated with AD care are likely to become economically unsustainable given the aging U.S. population, and therefore new cost-effective treatments are needed. Existing pharmaceuticals have provided only short-term symptomatic relief without affecting disease progression (16) and new drug development is excessively time consuming and costly. To address the paucity of effective AD treatments, we recently investigated the use of modest doses of ionizing radiation therapy as a novel treatment against amyloid pathologies associated with AD (17), since radiation has been successfully used to treat extra-cranial amyloidosis (18), with 5-year benefits (19). Using an AD mouse model (APP/PS1, cat. no. 005864; Jackson Laboratory, Bar Harbor, ME), we demonstrated that a single X-ray dose or a short course of fractioned X-ray doses significantly reduced the amyloid burden in the brain, with fractionation giving the most dramatic response as a function of delivered dose. The reduction in plaque burden was also associated with a decrease in the average size of the Aβ plaques; e.g., for 5 × 2 Gy X-ray irradiation, Aβ plaque size went from 42.95 μm² (SD ± 12.8) to 14.52 μm² (SD ± 11.6). These experiments were conducted using a hemi-brain irradiation technique, which allowed plaques to be assessed in the irradiated and nonirradiated side of the brain within the same animal. In further experiments, which used whole-brain irradiation, the reductions in amyloid plaques induced by 5 × 2 Gy irradiation were associated with improvements in cognition, as defined using the Morris water maze (17). While these initial data are intriguing, confirmatory studies are clearly still needed using other AD mouse strains and the duration

1 Address for correspondence: Department of Radiation Oncology, William Beaumont Hospital, 3811 W. Thirteen Mile Rd, 105-RI, Royal Oak, Michigan 48073; email: brian.marples@beaumont.edu.