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Chapter 10

The Confounding Factor of Apolipoprotein E on Response to Chemotherapy and Hormone Regulation Altering Long-Term Cognition Outcomes

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1. Introduction

One player in health cognitive functioning is shown to be lipoproteins, essential in the metabolism and redistribution of lipids: cholesterol, phospholipids and triacylglycerol. There are several classes of lipoproteins which are used to transport lipids throughout the body and range in density (protein/lipid ratio); chylomicrons (contain dietary lipids), intermediate low density lipoproteins (IDL), very low density lipoproteins (VLDL, bad cholesterol), low density lipoproteins (LDLs) and the high density lipoproteins (HDLs, good cholesterol). The Apolipoprotein/Apoprotein gene family of proteins is part of the lipoprotein complexes that function as regulators of binding between lipoproteins and receptors. These proteins act as enzyme co-factors during lipid metabolism, helping to stabilize lipoproteins during transportation from cell or tissue to its destination [1].

Apolipoprotein E (ApoE), initially termed the "arginine-rich apoprotein", was first identified as a part of the VLDL complexes. ApoE is synthesized principally in the liver, but has also been found in other tissues such as the brain, ovaries, lungs, adrenals, spleen, muscle cells, and macrophages [2]. The three most common alleles of *ApoE* are *ApoE2*, *ApoE3*, *ApoE4* [3] found in the nervous system are primarily produced in astroglia and microglia. The three major isoforms differ at position 112 (*ApoE2*/*ApoE3* Cysteine, *ApoE4* Arginine) and 158 (*ApoE2* Cysteine, *ApoE3*/*ApoE4* Arginine), the amino acid substitutions at position 112 affect salt bridge formation within the protein, which ultimately impacts on lipoprotein preference, stability of the protein and on receptor binding activities of the isoforms [4]. Being an *ApoE4* carrier or having the *ApoE2*/*ApoE3* genotype is associated with

higher triglyercide levels, higher VLDL levels, higher total cholesterol, higher total lipoproteins levels and elevated LDL or "bad cholesterol" levels all of which contribute to hypertension and diabetes confounding factors that have to be considered when designing a chemotherapy treatment regiment [5].

In rodent models, the lack of *ApoE* or ApoE4 protein expression leads to destabilization of cell membranes, increased apoptosis, and heightened sensitivity to neuronal trauma; whereas, ApoE3 and ApoE2 protein expression allow for healthy cell functioning and neuroprotection [4]. ApoE4 has detrimental effects in transgenic mice, including behavioral abnormalities, such as deficits in spatial learning and memory using Morris water maze (MWM) [6], as well as significant alterations in the hippocampus and cortex [4,7]. The studies in mice are consistent with clinical studies indicating reduced spatial learning and memory in those who carry the *ApoE4* allele [8]. Experiments have also demonstrated that the three isoforms of human *ApoE* gene have different effects on the development of neurodegenerative diseases. Those individuals that are *ApoE4* carriers have an increased risk of age-related mild cognitive impairments (MCI) and the development of Alzheimer's disease (AD) particularly in females [9].

In ovarian cancer, ApoE protein levels act as a potential tumor-associated marker as found in serous carcinomas, but not in serious borderline or normal ovarian surface epithelium cells [10]. Up-regulation of ApoE protein levels is also seen in breast carcinomas, pancreatic cancer, stomach carcinomas, colon carcinomas and prostate carcinomas [10]. Blockage of ApoE expression in the serous carcinoma cell lines leads to cell cycle arrest and apoptosis. Women infused with ApoE protein at the time of diagnosis showed significantly higher survival rates [10]. This data suggest that upregulation of ApoE expression may be a defense mechanism to help body fight carcinomas.

2. Chemotherapy, *ApoE* and memory

Over the last 20 years it has become apparent that chemotherapy drugs not only attack cancer cells, but also cross the blood brain barrier (BBB) leading to negative effects on cognitive processing which is known as Chemo-brain or Chem-fog [11,12]. Methotrexate, 5-Flourouracil (5-FU) the most common chemotherapy drugs used to treat breast, colorectal, head and neck cancers been shown in both rodent models and clinical studies to lead to neurocognitive deficits in a variety of domains including visual memory and visuospatial functioning [11,13,14]. In clinical studies, there is considerable variability between studies as to the extent and frequency of such impairments heretofore mentioned. However, rodent studies are clearly show that the drugs in the CMF (cyclophosphamide, methotrexate, 5-FU) regiment lead to decreased hippocampus cell proliferation and induce MWM memory impairments [15,16]. In addition, cytarabine (cytosine arabinoside) and ifosfamide among other chemotherapy have been shown to lead to memory impairments, hemiparesis, aphasia and progressive dementia [17]. However, there is significant lack of pre-clinical testing of most chemotherapeutic agents and their long-term effects on memory.

Currently, only one study has examined if *ApoE4* carrier status as a potential genetic risk factor in breast or lymphoma survivors. They have found that even after 8 years, *ApoE4* carriers displayed impairments, specifically in visual memory and spatial ability [18]. This suggests that the *ApoE* genotype may be a confounding factor to consider when examining post-chemotherapy neurocognitive status. More studies are necessary to confirm this result.

Studies in women treated with CMF regiment for breast cancer found increased total cholesterol, LDL, HDL cholesterol and Apolipoprotein A-1 (ApoA-1) in those who developed permanent amenorrhea (loss of menstrual cycle, induced menopause) [19]. Studies report that around 30% of patients who have gone through chemotherapy develop permanent amenorrhea [20]. There is evidence that *ApoE4* carriers have an earlier onset of natural menopause [21]. Age of menopause and being an *ApoE4* carrier are both risk factors for age related diseases including AD and coronary artery disease (CAD). There is also a direct connection between ApoE mRNA levels and estrogen in various tissues, including the brain [22] leading to regulation of neurite outgrowth [7]. The data suggests that ApoE is a critical intermediary in the estrogen related neuroplasticity [7]. Lack of estrogen along with expression of ApoE4 protein which has reduced ApoE functioning is one potential cause of impaired cognitive performance in some women that have undergone chemotherapy. Studies do not take this factor into account or narrowly examine menopausal status at the time of testing.

3. Apolipoproteins effects on secondary drug response

3.1. Tamoxifen

Other confounding factors that can affect cognitive status after chemotherapy include other medications patients are taking to control comorbid conditions or to treat the tumor itself. Tamoxifen is used as an estrogen receptor modulator (SERM) in estrogen receptor (ER) positive breast cancer carcinomas. Tamoxifen is a pure estrogen receptor blocker. As with other drugs, tamoxifen and its metabolites can cross the BBB affecting ER in various brain regions including the cerebral cortex, hippocampus and amygdala [23]. In combination with chemotherapy, tamoxifen appears to intensify the cognitive impairments, particularly in visual memory, verbal working memory and visuospatial ability [24]. The Anatrozole, Tamoxifen Combined (ATAC) trial, also found verbal memory and processing speed impairments post-chemotherapy treated only with tamoxifen compared to women only on a combined ATAC treatment (Table 1) [25]. This suggests that tamoxifen has confounding effects when given as part of the chemotherapy regiment. Tamoxifen also appears to have both agonist and antagonist properties in the brain with reported up-regulation of pro-inflammatory cytokines shown to be related to cognitive dysfunction [26]. Positron emission tomography (PET) imaging of survivors does show higher hypometabolism with dual chemotherapy and tamoxifen, not seen in women treated only with tamoxifen [27]. Animal models using repeated tamoxifen or combinations of methotrexate and 5-FU injections both produced deficits in acquisition and retention in an operant learning paradigm (Table 1)

[28]. These studies were conducted when women were still in treatment, leaving the question of potential long-term effects. There is a study that examined women who used tamoxifen for <4 years compared to >6 years of exposure. The study found that the current exposure led to greater memory deficits compared to non-users (Table 1) [29]. This suggests that while on therapy, patients may have acute memory impairments and that alternative drugs should be seriously considered.

In breast cancer survivors undergoing tamoxifen treatment, their total cholesterol, VLDL, high density lipoproteins (HDL) and Apolipoprotein B (ApoB) protein levels have been shown to decrease in both *ApoE4* carriers and non-*ApoE4* carriers (Table 1) [30,31]. Breast cancer patients who are *ApoE4* carriers have higher plasma triglyceride levels and altered ApoA-1/ApoB ratio. Both are risk factors for cardiovascular events, after tamoxifen treatment (Table 1) [30,31]. In non-*ApoE4* carriers, there were lower levels of lipoprotein (a) after treatment, but no effect on triglycerides or the ApoA-1/ApoB ratio (Table 1). This suggests that non-*ApoE4* carriers have a more positive response to tamoxifen with respect to lipid profiles and risk for cardiovascular complications [31]. Considering tamoxifen and *ApoE4* both have a deleterious effect on cognition and tamoxifen has an *ApoE* genotype dependent effect on lipid profiles, suggest further investigations are warranted to understand the mechanistic relationship.

3.2. Anatrozole

Anatrozole also known as arimidex is an aromatase inhibitor that lowers estrogen levels and is used as a treatment in estrogen positive breast cancer patients post-surgery. Results of the ATAC trial of 9399 women indicated that those only on arimidex had better clinical outcomes including vascular events and gynecological problems compared to the tamoxifen group with no differences seen in cognitive outcomes [25,32]. There data suggests that arimidex was the preferred initial treatment by women treated for breast cancer [32]. However, other studies indicate that women on arimidex treatment had greater cognitive decline than tamoxifen treatment in verbal and visual memory (Table 1) [33,34]. At this point no effects have been seen on cholesterol, lipoproteins or apolipoprotein levels in both animal models and clinical studies (Table 1) [35,36]. Although, there are not alternations in lipids levels, the cognitive side effects are of concern with this medication and should be examined with respect to *ApoE* genotype.

3.3. Letrozole

Letrozole, a potent aromatase interfering with adrenal steroid biosynthesis, has also been assessed as a replacement for tamoxifen or as secondary maintenance treatment after tamoxifen as part of the Breast International Group (BIG 1-98) trial [37,38]. In the BIG 1-98 study, better overall cognitive outcomes were seen in women on letrozole treatment compared to those on a tamoxifen treatment (Table 1) [37,38]. In the tamoxifen only group, increased endometrial cancer and vaginal bleeding where found [38]. Participants given letrozole only did displayed more incidences of skeletal and cardiac events and

hypercholesterolemia compared to the tamoxifen group [37]. After letrozole treatment, unfavorable effects have been seen including increased serum total cholesterol, LDL and ApoB with atherogenic ratio risk of total cholesterol/HDL and LDL/HDL levels (Table 1) [39]. Therefore, the better cognitive outcomes may not out-weigh negative effects on lipoprotein levels, particularly in those with or at risk for hypertension and/or diabetes. The potential confounding factor of *ApoE* genotype has not been reported.

3.4. Exemestane

There is another alternative for estrogen suppression therapy exemestane, an aromatase inhibitor, general used after tamoxifen is not working in post-menopausal women. Exemestane has been examined as part of the randomized Tamoxifen and Exemestane Adjunctive Multinational (TEAM) trial [24]. The preliminary data from the TEAM trial found that tamoxifen is associated with lower verbal and executive function, while exemestane did not seem to alter cognitive performance levels (Table 1) [24]. Analysis of data from 72 patients as part of the EORTC trail 10958 indicates that treatment with exemestane resulted in reduced triglyceride levels and tamoxifen treatment increased triglyceride levels [40]. All other lipid parameters including HDL, ApoA-1, ApoB or Lip (a) levels at 8, 24 and 48 weeks were unchanged by either treatment [40]. Further studies will be needed to determine if stable cognitive performance and lipid levels are effect of *ApoE* genotype.

3.5. Raloxifene

Raloxifene, also a SERM and is used as a hormone replacement therapy, has the positive effects of estrogen on the skeletal system and is an antagonist of estrogen in breast or endometrial tissues [41]. Raloxifene treatment also appears to be less detrimental to cognitive function assessed by Modified Mini-Mental State (3MS) compared to tamoxifen [42]. Used to prevent osteoporosis, it has been shown that after three years of treatment raloxifene did not affect overall cognitive scores [43]. The Multiple Outcomes of Raloxifene Evaluation (MORE) study of 7478 women, reported finding that raloxifene treatment lowered the risk of cognitive decline in word list recall test and there was no overall effect on cognitive function (Table 1) [44]. A subset of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR), the CoSTAR study for women at high risk for breast cancer did not find any cognitive effects of either drug (Table 1) [45]. Together the evidence supports that raloxifene treatment does not impair cognitive function the way that tamoxifen treatment and in fact may even lower the risk of cognitive decline [34].

With respect to lipid and lipoprotein levels post hoc analysis of 2659 women in the MORE study, found that raloxifene treatment in women with or without high triglycerides lead to reduced cholesterol levels with healthier lipoprotein parameters (Table 1) [46]. Studies in Greek women, found that LDL cholesterol levels were lower in women treated with

raloxifene [47]. Raloxifene also appears to raise HDL levels and ApoA-1 while decreasing ApoB protein levels and improving ratios of total cholesterol to lipoproteins (Table 1). After one year of treatment with raloxifene women had reduced fat mass and trunk and central regions along with decreased adiposity in their truck and abdominal regions (Table 1) [48]. Overall, raloxifene treatment improves cholesterol health and alters fat distribution in a positive manner to help prevent obesity, making it a better candidate for overall health compared to tamoxifen. Its effects in relation to *ApoE* genotype have not been reported.

3.6. Estradiol

In post-menopausal estradiol (also known as 17β-estradiol or oestradiol) treatment is used for estrogen replacement therapy. Healthy post-menopausal women given estradiol display improved visuospatial abilities measured by a mental rotation task (Table 1) [49]. Other non-randomized studies in women with surgically induced amenorrhea or those with AD indicate that estrogen replacement treatment may help to improve or minimize cognitive deficits [50]. Even in men those given estradiol performed better on visual memory after treatment (Table 1) [51]. These results are consistent with improved memory in mice given other replacement estrogens treatments [52]. Over half of randomized clinical studies find significant improvements in cognition and attention after estrogen replacement therapy (Table 1) [53]. Estradiol has been shown to increase levels of ApoE in the brain, proposed to be beneficial for neuronal reorganization and repair [7]. In a health study of 3,393 women, results suggest that estrogen replacement reduces the risk of age-related cognitive decline in non-*ApoE4* women, but not in *ApoE4* carriers (Table 1) [54]. Another study with 181 post-menopausal women, also found the best learning and memory performance after estrogen replacement is seen in non-*ApoE4* carriers [55]. This suggests that knowing *ApoE* genotype may be helpful to assess potential response to estrogen replacement therapy.

Treatment	**Function**	**Effects on Lipids/Apolipoproteins**	**Effects on Cognition**
Tamoxifen	Estrogen receptor modulator (SERM) lowers estrogen function	Decreased total cholesterol, VLDL, HDL and ApoB protein levels.	Leads to impairments in visual memory, verbal working memory and visuospatial ability.
Anatrozole	Aromatase inhibitor lowers estrogen function	No effects seen in rodent or clinical studies.	Reduced verbal and visual memory compared to tamoxifen. Deficits

Treatment	Function	Effects on Lipids/Apolipoproteins	Effects on Cognition
			in rodent model operant learning paradigm.
Letrozole	Aromatase inhibitor lowers estrogen function.	Increased serum total cholesterol, LDL and ApoB increase risk of cardiovascular events.	Better overall cognitive outcomes compared to tamoxifen treatment.
Exemestane	Aromatase inhibitor lowers estrogen function.	Reduces triglyercide levels.	No effect on cognitive performance compared to Tamoxifen group that had lower verbal and executive functioning.
Raloxifene	SERM, lowers estrogen function in reproductive tissue and used as estrogen replacement therapy in non-reproductive tissues.	Lower cholesterol, LDL, ApoB protein levels and increases ApoA-1, HDL level leading to better cardiovascular health. Also shown to reduced adiposity and fat mass.	Lowered the risk of cognitive decline or has no effect.
Estradiol	Estrogen replacement therapy	Increase ApoE protein levels in brain. Reduces cognitive decline in only non-*ApoE4* carriers.	Treatment improves visuospatial abilities and visual memory.
Tibolone	Estrogen replacement therapy	Reduces total cholesterol, triglyceride levels, HDL and ApoA-1 levels.	Decreased anxiety, improved quality of like and semantic memory.
Cetrorelix	Used to reduce gonadotrophins and sex steroids	Increases ApoA-1 and HDL levels.	Anxiolytic, anti-depressive and improved beta-amyloid 25-35 associated memory consolidation impairments.

Table 1. Hormone treatments effects of lipids/apolipoproteins levels and cognition.

3.7. Tibolone

Tibolone is another drug used in hormonal replacement therapy having estrogenic, progestogenic, and androgenic effects. Long-term treatment does appear to decrease anxiety, improve semantic memory and overall quality of life; however, one study reported that those in treatment did score worse on attention task compared to women not on treatment (Table 1) [56,57]. Tibolone appears to be the most beneficial with respect to reducing total cholesterol, triglyercide, HDL and ApoA-1 levels compared to raloxifene and estradiol (Table 1) [47,58-60]. This suggests that hormone replacement therapy with medications such as tibolone in post-menopausal women are beneficial to cognitive health and lipid profiles.

3.8. Cetrorelix

Cetrorelix an antagonist of hypothalamic luteinizing hormone-releasing hormone (LHRH), is used in treatment of prostate carcinoma, benign prostatic hyperplasia, and ovarian cancer to reduce gonadotrophins and sex steroids [61]. In mice, a study suggests that it is anxiolytic, anti-depressive and able to correct beta-amyloid 25-35 associated memory consolidation impairments (Table 1) [61]. Injection of cetrorelix into *ApoE* deficient mice (*ApoE*$^{-/-}$) mice suggests that the associated suppression of testosterone leads to increased atherosclerosis despite lower cholesterol levels in the male mice [62]. In female *ApoE*$^{-/-}$ mice, the reduction in testosterone also leads to reduction in estradiol, insulin and HDL levels without effects on atherosclerosis [62]. In a pilot study conducted in men, treatment with cetrorelix resulted in increased ApoA-1, HDL, insulin and leptin consistently (Table 1) [63]. Therefore, when this drug is used within a chemotherapy treatment regiment it is important to carefully monitor lipid levels. Additional studies are needed to examine if *ApoE* genotype has any effect on response and potential long-term cognitive side effects of this drug.

4. Recommendations

1. Determine if an *ApoE* genotype can help assess what is most treatment useful including how to properly maintain lipid levels during chemotherapy.
2. Find out lipid levels, track and maintain determined treatment to reduce risk of post-chemotherapy cognitive impairments.
3. Examine *ApoE* genotype before selecting pharmacotherapy options pre or post-chemotherapy treatment.

5. Conclusion

Overall of the studies SERMs/aromatase inhibitors raloxifene or exemestane may be better alternatives to tamoxifen or letrozole treatment in terms of effects on cognitive deficits and overall health risk in women treated with chemotherapy. In addition, *ApoE* genotype and cholesterol levels need to be taken into account when examining efficacy of these drugs and

in hormone replacement therapies as efficacy is dependent on *ApoE* genotype. Knowing these issues will help doctors to address them early for improving quality of life, reducing services used and saving millions of dollars in unneeded medical expenses. Realistically, the wonder drug that can cure all cancer and has no side effects will not be found. What is needed is to reduce the impact and intensity of cognitive side-effects as much as possible, taking into account an individual's physiology and genetics. The more we know about cognitive status across ages, ethnicity, lipid levels, and genetic status the better we can treat mind and body.

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