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Breast cancer nutritional chemistry cachexia oncology – A clinical trials perspective

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Breast cancer is the second largest killer disease among women globally. Annually approximately 48,000 women die of breast cancer. Breast cancer patients are at high risk of developing malnutrition from the underlying disease as well as from various drug regimen, chemotherapy and or radiotherapy interventions. As we work for personalized medicine for breast cancer, a personalized nutrition for breast cancer patients is much needed for their wellbeing both physiologically and psychologically. Most rather than all, of the treatment regimens possesses a concourse of side effects. An effective personalized nutritional therapy during and after cancer treatment leads to better quality of life for the breast cancer patients. Clinical trials are pivotal for any recommendations to be used at the commercial level upon approval of Food & Drug Administration. Several clinical trials have been carried out and many are now undertaken to come up with a significant upshot conclusion based on primary and secondary outcomes to show the after effects of particular nutrient supplements by increasing the overall survival or any other physiological upregulated / downregulated manifestation leading for a disease free survival. Docosahexaenoic acid and glutamine nutritional supplement has been reported to have beneficial effect for breast cancer patients in different clinical trials.

Keywords: Breast cancer, Nutrition, Docosahexaenoic acid, Glutamine

Designing a personalized with a precision for breast cancer patients in a truly clinical nutrition intervention is considered as the cutting-edge technology solution for the disease-free survival of the breast cancer patients. The oncologist in such a therapy has to work together with the nutritionist to reach up to the patient, patient's caretakers and also to a multiconvergence team comprising of data analysts, nursing fraternity and health counsellors to provide an adequate nutritional assessment based on the breast cancer patient's preference to come up with the intervention follow-up[1,2]. Several start-ups for breast cancer therapy and prognosis work on convergence technology as focus groups for the reduction of breast cancer mortality[3]. Metformin a well-known drug for diabetes is now in the clinical trials for breast cancer therapy, as we want a solution from all directions of technology development and developers[4]. In terms of breast cancer diagnosis, Raman spectroscopy is in the pipeline for more accurate early detection of breast cancer[5].

Materials and Methods

Docosahexaenoic acid

Dietary docosahexaenoic acid (DHA) (Fig. 1A) can make mammary tumours more sensitive to anti-cancer agents. Omega-3 fatty acids especially DHA belongs to polyunsaturated fatty acids category which are long-chained. Their long chain are basically and most predominantly alpha-linolenic acid, which possess 18 carbon chain back bone. DHA is abundantly found in sea foods. Normal physiology of a human being produces DHA under regular and normal metabolic conditions, upon triggering the normal physiology due to cancerous condition leading to morbidity, the quite normal metabolic cascade goes hayward resulting in cachexia. Absorption of DHA by the human system and these nutrient molecules reaching out for the cellular uptake is without an iota of doubt it is only by direct intake and consumption of food containing rich sources of DHA. Levels of DHA in blood plasma concentration can be worked upon by the nutritional food regime to the breast cancer patients. Double the plasma concentration of DHA has also been achieved by a scheduled nutritional menu for breast cancer patients. This increase in blood plasma DHA concentration leads to fecundation of lipids present in plasma membrane.

Glutamine

Plethoric quantum of Glutamine (Fig 1B) is freely available in as a free amino acid in the biological fluids and specimens especially blood plasma and tissue. Breast cancer consociated complexities primarily cachexia and dermal damage post

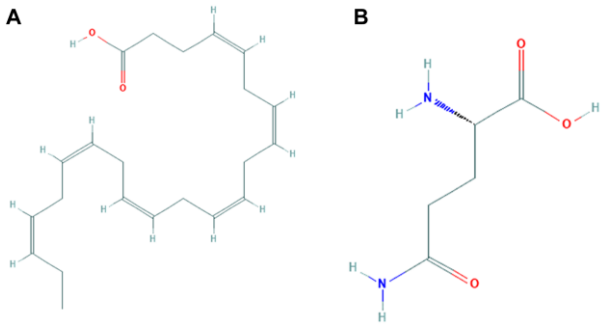

Fig. 1 — Structure of (A) docosahexaenoic acid (B) Glutamine

radiotherapy is very much associated with shrivelled concentration amounts of amino acids in the blood circulation, especially Glutamine. By increasing the blood plasma glutamine concentration, acts as a immune booster for some subtypes of breast cancer.

Results and Discussion

Several clinical trials have been carried out, recruiting and many in the pipeline for the effect of DHA on the clinical outcomes in a modified primary, secondary and exploratory outcomes. The outcomes of a clinical trial need to be quantitative and statistically significant for the elucidation of a clinical trial. There are several outcome definitions of a clinical trial namely, disease free survival, overall survival, variation of a biochemical biomarker, recurrence incidence and so on.

Generally, for a nutritional supplement-oriented chemotherapy, regular drug regimen is followed for both the standard (control) ARM and the test ARM. ARM-1 being provided with a placebo and ARM-2 to be provided with DHA rich nutritional supplement in the form a food intake rather as a therapeutic.

Enhancement of chemothrapy efficacy was evaluated[6] by carrying out a double-blind, phase II randomized clinical trial. Total numebr of recruiters were 52 in total with an expected 10% dropout. ARM-2 (n = 23) being the test ARM were provided with 4.4 g/day DHA orally. The placebo ARM-1 (n = 23) was prescribed with the same quantity and amount as ARM -2 but of vegetable oil which are rich in fat supplement. Differences in Ki67 labelling index identified by biopsy studies (core needle) before chemotherapy was the primary outcome with several biochemical biomarkers variation with respect to the placebo ARM were the exploratory outcomes one of the chief augmenting the primary outcome being DHA plasma phospholipid content.

In ARM-2 the test ARM having the DHA supplementation, one other evaluation was also carried out as an inter ARM elucidation upon a statistically significant proposition was observed wherein the difference in DHA the factors influencing the incorporation upon a comparison (low versus high incorporators) possible factors that predict incorporation was also studied. As this clinical trial is still underway, interesting results are awaited (Clinical Trial Registration Number NCT03831178).[7]

In another clinical trial (Phase II)[8] involving 25 breast cancer patients (n = 25) were studied for the effect of DHA nutritional supplement. This phase II clinical trial recruited metastatic breast cancer patients undergoing anthracycline chemotherapy drug regimen for the elucidation of the efficacy and safety intake amounts of nutritional supplement of DHA. In addition, among the twenty five recruited breast cancer patients, twelve breast cancer patients had received tamoxifene as an adjuvant hormonal therapy. The median age is being 52 years of old in the range of 32 to 71. Minimum dosage of 1.8 g/day of DHA is needed wherein less than this stipulated concentration will not elicit a physiological and biochemical incorporation of the intake of DHA into tissue cell membrane phospholipids. This is a single ARM clinical trial. All the breast cancer patient recruiters were prescribed nutrient supplement DHA enriched capsules containing triglyceride oil of algal origin (44% DHA providing minimum 0.2 g DHA). Daily dosage of nine capsules which is representing 0.2 g of DHA for a daily intake is surmounting a needed intake of 1.8 g/day of DHA.

In this open-label single-arm phase II study, single inter ARM strategy was used for the evaluation of the primary and secondary end points. Patient distribution according to the extent of DHA increase was segregated as Low DHA incorporators (L-DHA) and High DHA incorporators (H-DHA). Different primary and secondary end points are considered for clinical trials. In this clinical trial, response rate was one of the primary end point and safety profile was the other primary end point. Time to Progression (TTP) and overall survival (OS) were the secondary end points. Response was defined as complete response (CR), partial response (PR), stable disease (SD) and / or progressive disease (PD).

$$\text{Objective Response Rate (ORR)} = \frac{\text{CR} + \text{PR}}{\text{n}} \quad \ldots (1)$$

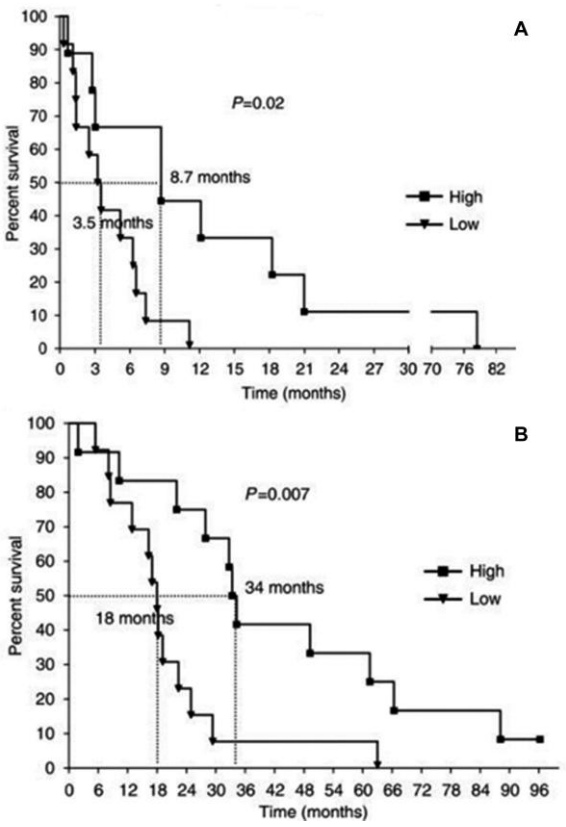

Fig. 2 — (A) Time To progression (TTP) and (B) profile of ARM -1 and ARM -2 (*Ref. 8*)

$$\text{Clinical Benefit (CB)} = \frac{\text{CR} + \text{PR} + \text{SD}}{\text{n}} \quad \ldots (2)$$

Where, n = number of patients. ORR was calculated and found to be 44% (95% CI, 24.5–63.5) (1 CR and 10 PR) with eleven SD cases and three PD cases. CB was also calculated and observed to be 88%.

One of the secondary endpoint namely, OS was the most impressive finding in this clinical trial using metastatic breast cancer patients. TTP was significantly higher in patients with an H-DHA incorporation (8.7 months vs 3.5 months) in patients with L-DHA incorporation), suggesting a greater efficacy of chemotherapy (Fig 2A) .OS was almost doubled in patients with H-DHA incorporation (34 months vs 18 months) (Fig 2B).

Improvement of treatment outcomes for breast cancer patients who were prescribed and underwent radiotherapy, certain dermal damages and injuries could be protected or at the minimization level has been studied using glutamine as a nutritional supplement. Dermal texture and level of cosmetic disfiguration has been quantified. Recurrence of these dermal effects was also studied. A positive trend in the direction of subsiding effects of skin radiation injury and pain was observed.

In this randomized double-blind study[9] totally seventeen breast cancer patients for whom radiotherapy as the first line of treatment for their health issue were recruited. ARM -1 the control ARM having n = 8 were placed in the placebo Arm and rest n = 9 were placed in the test ARM -2. Dextrose was given for ARM -1 and Gln for ARM -2. The patients were randomized to receive one of the oral nutritional supplement which was thoroughly mixed and shaken in a cold liquid of the preference of the recruiters either pure amino acid L-Gln powder (0.5 g/kg/d) or dextrose, 25 g/d). Radiation Therapy Oncology Group (RTOG) scales were used for the evaluation of radiation injury occurred due to radio therapy intervention. In a scale of 0 – 4 for acute radiation morbidity scoring criteria now changed to acute necrosis. Cosmetic scores were also evaluated. Other biomarkers and biochemical parameters were also quantified like blood glutamine, glutathione (GSH) and serum protein profiling.

Conclusions

Many more clinical trials in nutritional cachexia oncology are needed especially for breast cancer patients to reduce the mortality. Henceforth, a holistic personalized care is mandatory to reduce breast cancer mortality by 50% by 2035.

Conflict of interest

The authors declare no conflict of interests in this study.

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