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Tidal chemotherapy in premenopausal patients with hormone receptor positive breast cancer

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ABSTRACT

Neoadjuvant chemotherapy remains an inseparable part of systemic therapy for hormone receptor positive (HR+) advanced breast cancer. However, efficacy of neoadjuvant chemotherapy in this subtype of patients is inferior to its hormone receptor negative counterpart. Several preclinical and clinical studies have suggested that it was growth rate rather than hormone receptor status that determined sensitivity to chemotherapy. In addition, estrogen was proved to recruit more HR+ breast cancer cells into actively dividing phase according to various studies. For premenopausal females, sexual hormone like estradiol fluctuates with menstrual cycle. When menstruation occurs, women have the lowest level of estradiol, which is resemble to pharmaceutical effect of endocrine therapy. If chemotherapy is given to females during menstruation, it's almost equal to concurrent use of chemotherapy and endocrine therapy, which is not recommended by guideline. Accordingly, chemotherapy would attain best efficacy applied at the peak of estradiol, because more tumor cells being in actively dividing phase recruited by comparatively high level of estradiol would help cytotoxic agents function better given that majority of chemotherapeutic drugs are cellular phase dependent. We name this rhythmic mode of chemotherapy for premenopausal HR+ breast cancer females, giving chemotherapy to patients when estradiol rises and avoiding prescription at menstruation, tidal chemotherapy. It's postulated that tidal chemotherapy would improve efficacy of neoadjuvant chemotherapy for premenopausal HR+ breast cancer females, achieve more pathologic complete response and in the long run improve prognosis.

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Background

In 2016, it's estimated that 246,660 new cases will be diagnosed with breast cancer in the U.S, which was the most prevalent malignant tumor in females. When new cases were stratified by age, 10.7% of them were distributed before age of 45 [1]. Not that frequent in young population as it is with elder ones, breast cancer still accounts for 30–40% of all cancer events in females younger than 40 [2]. It's widely acknowledged that young age has an adverse effect on the prognosis of breast cancer, either attributed to later stage at initial diagnosis [3] or unfavorable biomarker of the tumor [3–5]. However, even having adjusted for stage, histopathological characteristics and treatment, young age remained an independent negative prognostic factor [6]. More aggressive systemic treatment is indicated in this group of patients, including operation, adjuvant chemotherapy, radiotherapy, etc [6]. Hormone receptor positive (HR+), defined as estrogen receptor (ER) and/or progesterone receptor (PR) positive, is commonly observed in young breast cancer patients, less likely than in aged patients, though [7,8]. For HR+ advanced breast cancer, preoperative neoadjuvant chemotherapy is frequently applied to lower tumor stage to create opportunity of resection in inoperable patients as well as to shrink tumor volume permissible for breast conservation surgery. Furthermore, it has been suggested in several studies that pathologic complete response (PCR) attained through neoadjuvant chemotherapy was an indicator for prolonged disease free survival (DFS) and overall survival (OS) [9,10] while simply increasing courses of chemotherapy wouldn't help create more PCR [11]. Nevertheless, HR+ advanced breast cancer tended to benefit less from neoadjuvant chemotherapy compared with HR- counterpart [12–14] and PCR was apparently less likely as well [15]. How to improve efficacy of neoadjuvant chemotherapy in young patients with HR+ advanced breast cancer is a problem demanding prompt solution.

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Approaches to improve efficacy of neoadjuvant chemotherapy

Determination of efficacy of neoadjuvant chemotherapy

Since PCR was a good predictor for prolonged DFS and OS compared with patients with residual focus after cycles of neoadjuvant chemotherapy [16–18], nowadays there were studies deeming PCR as parameter of favorable prognosis for advanced breast cancer undergoing neoadjuvant chemotherapy with much shortened follow-up period [19]. Why does HR+ breast cancer profit less or even null from neoadjuvant chemotherapy? Sueta et al. preformed a retrospective study investigating the value of pre-chemotherapy Ki67 in prediction of pathological response across different subtypes of breast cancers [20]. And Ki67 was found to be an independent marker for PCR after neoadjuvant chemotherapy, when stratified by ER status such association was restricted to ER+ subtype [20]. This phenomenon was accorded in some studies [21,22]. With Ki67 having been reported to correlated to proliferation rate of tumor [23,24], it is postulated that proliferation rate of breast cancer tumor cells determines response to neoadjuvant chemotherapy for HR+ advanced breast cancer. In a preclinical study, it was demonstrated that efficacy of chemotherapy for breast cancer was associated with growth rate rather than ER status [25]. In this study, growth rate of ER+ cells was slower compared with ER- counterpart originally, and when cell culture medium was altered to achieve same proliferation rate in ER + and ER− cell lines, sensitivity to paclitaxel was comparable [25], which verified the postulation that proliferation rate of breast cancer cells rather than HR status determined sensitivity to neoadjuvant chemotherapy for advanced breast cancer. Given this premise, better efficacy of neoadjuvant chemotherapy for HR + advanced breast cancer is attainable by accelerating growth rate of tumor cells.

Chemosensitizing role of estrogen

For HR+ breast cancer, endocrine therapy is an inseparable part of systemic therapy [26]. Theoretically, it is generally accepted that endocrine therapy works by a silencing mode preventing tumor cells from cycling actively. Other cells apoptose normally. Taken together, the volume of tumor shrinks. On the contrary, majority of cytotoxic drugs work better on cells dividing more actively or more proportion being in division phase. Therefore, it was logical that chemotherapy and endocrine therapy couldn't function in a synergic way and guideline doesn't recommend concomitant use of two regimes [26].

Under physiological condition, premenopausal females have sexual hormone fluctuating with menstrual cycle (Fig. 1). During uterine cycle of menstruation, initial 2–7 days of follicular phase namely, estradiol level is below 50 pg/ml. When ovulation happens, the estradiol level can be as high as 250 pg/ml and thereafter there is a plateau around 150 pg/ml in luteal phase. If chemotherapy is applied during the valley of estradiol in menstrual cycle, the internal environment is resemble to pharmaceutical effect created by endocrine therapy, which is equal to concurrent use of endocrine therapy and chemotherapy. However, simultaneous application of two modality is not recommended according guideline [26]. Estradiol of valley value would halt HR+ tumor cells from entering actively dividing phase further compromising sensitivity to chemotherapy.

From the other perspective of the problem, can add-back of estrogen to the culture medium or physiological condition restore sensitivity to chemotherapy in HR+ breast cancer? In vitro, culture of ER+ MCF-7 cells in estrogen deprived medium resulted in 90% of the cells in dormant state, G0/G1 phase of cell cycle namely. When estradiol was added to the medium, tumor cells metabolized more actively and turned to S-G2/M phase further. For estradiol preincubated MCF-7 cells, chemotherapy functioned better compared with unstimulated controls [27–29]. Adoption of this theory in clinical practice had led to controversial results in comparatively earlier studies. However, owing to defect in study design, effect of estrogen as a chemosensitizer for HR+ breast cancer might have been underestimated [30–33].

Hypothesis

Patients with HR+ advanced breast cancer benefit less or even null from neoadjuvant chemotherapy compared with HR- counterparts. Aside from genetic factor [34], majority of tumor cells of HR + breast cancer being in retarded or stagnant phase might have also played a role [35]. Thus, in order to improve effect of neoadjuvant chemotherapy for advanced HR+ breast cancer, collection of more tumor cells in actively proliferating phase seems the main solution. Estrogen has been proved to facilitate transfer of HR + breast cancer cells from G0/G1 phase to S-G2/M phase [28,36]. Therefore, it's rational to postulate estrogen also had a chemosensitizing role for HR+ breast cancer. Premenopausal females have endogenous estrogen fluctuating with menstrual cycle. If chemotherapy is applied during the valley of estradiol in menstrual cycle, the tumor cells are indolent and less portion is in S-G2/M phase. Therefore, effect of chemotherapy is not satisfactorily achieved. It may be deemed as concurrent use of hormone therapy and chemotherapy, which is not recommended by guideline [37]. Thus, oncologists should avoid giving chemotherapy to their premenopausal patients with HR+ advanced breast cancer at menstruation. Accordingly, chemotherapy would play its best when it's given at the peak of estradiol. In premenopausal HR+ advanced breast cancer patients, chemotherapy should be administered around ovulation calculated through last menstrual period (LMP) for the first several courses when chemotherapy induced amenorrhea (CIA) hasn't taken place. When CIA finally occurs or menstrual disorder arises, even though there isn't visible menstruation, fluctuation of estradiol may still exist. Detection of ovulation through evaluation of sexual hormone would help compensate and prescribe chemotherapy accordingly. Given that there isn't visible menstruation or fluctuation of estradiol, exogenous supplement of estradiol could still act similar way as under physiological circumstance. Comparatively high level of estrogen help gather more tumor cells in S-G2/M phase, sensitize cytotoxic function and achieve more PCR in HR+ advanced breast cancer. With PCR indicating better prognosis in the long run, application of neoadjuvant chemotherapy under this modality might lead to longer DFS and OS. We name this chemotherapy mode, administration of chemotherapy as estradiol level rises and avoidance of application during the valley of hormone in premenopausal HR+ advanced breast cancer patients, tidal chemotherapy because it's assemble to tidal rhythm. It's hypothesised that tidal chemotherapy could help collect more tumor cells in actively dividing cellular phase and have a chemosensitizing effect on HR+ tumor cells, generate better prognosis further.

Evaluation of the hypothesis

In 1988, Bontenbal et al. investigated role of estradiol when given prior to doxorubicin in MCF-7 cell line. Concentration of 30 pM of estradiol preincubating MCF-7 for 18–24 h led to 3–5 times the original ratio of tumor cells in S-G2/M phase. Augmented uptake of doxorubicin was observed after incubation tumor cells in the medium for 6 h and better control of tumor proliferation was achieved. Taken together, this preclinical study indicated that

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