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Review Article

Concurrent administration of ovarian function suppression and adjuvant endocrine treatment for premenopausal early breast cancer

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Abstract: Adjuvant endocrine therapy with tamoxifen for 5 years has been golden standard for hormone receptor (HR) positive premenopausal breast cancer patients. As yet, it is unclear what impact of ovarian function suppression (OFS) will have on patients who receive adjuvant tamoxifen therapy, though OFS is effective in the treatment of advanced breast cancer. The recent report of SOFT trial showed concurrent administration of OFS and tamoxifen could improve DFS in women at sufficient risk to warrant adjuvant chemotherapy. According to the conjoint analysis of the SOFT and TEXT trials, the application of aromatase inhibitor plus OFS represents an additional therapeutic option for HR positive premenopausal breast cancer patients. Here, we discuss recent outcomes of OFS in combination with tamoxifen or aromatase inhibitor in premenopausal candidates with HR responsive breast cancer. In addition, the indication, duration and side effect of OFS are also illuminated in this review.

Keywords: Breast cancer, endocrine therapy, ovarian function suppression, tamoxifen, aromatase inhibitor

Introduction

Approximately 25% of women with breast cancer are diagnosed before 50 years old, and about 60% of premenopausal breast cancer have a tumor expressing estrogen receptor (ER) and/or progesterone receptor (PR) are candidates for hormonal therapy [1]. Adjuvant treatment for premenopausal women with endocrine responsive disease is often a matter of debate. Chemotherapy, tamoxifen, and ovarian function suppression or ablation are individually effective adjuvant treatments for women under 50 years with ER-positive breast cancer [2, 3]. Five years of tamoxifen reduces the odds of recurrence by 40% when added to adjuvant chemotherapy [4, 5]. OFS shows similar efficacy to CMF chemotherapy in the absence of tamoxifen, and the question of whether there are any advantages to combining OFS with tamoxifen for premenopausal women has garnered a great deal of interest. Several studies have attempted to answer this question, but the results have been inconsistent [6-9]. Aromatase inhibitors (AIs) are superior to tamoxifen for postmenopausal women with endocrine-responsive breast cancer [10-17]. But, in the high estrogen environment of young women they would not be effective if women retain, or regain ovarian function under AI therapy [18]. Treatment with OFS provides an opportunity to test whether AIs can also improve clinical outcomes for premenopausal women.

Whether to add OFS to combined tamoxifen and chemotherapy for premenopausal women with breast cancer is the question most relevant to current practice. Here, we will review available data on following aspects: (1) concurrent administration of OFS and tamoxifen (2) concurrent administration of OFS and an aromatase inhibitor (3) the indication, duration and adverse events of OFS.

Concurrent administration of OFS and tamoxifen

Compared with no adjuvant therapy, OFS reduces the risk of recurrence and mortality by 31% and 28%, respectively [19]. OFS and chemotherapy have demonstrated similar efficacy in

Table 1. Tamoxifen + OFS versus tamoxifen alone

Study	Time of enrolling	Treatment arm	No. Of patients	5-years DFS (%)	5-years OS (%)	DFS HR (95% CI)	OS HR (95% CI)
ZIPP [24]	1987	Tam	879	NR	NR	0.69* (0.57-0.83)	0.72* (0.58-0.90)
		OFS	469	NR	NR	0.66* (0.53-0.81)	0.71* (0.55-0.92)
		Tam + OFS	882	NR	NR	0.63* (0.52-0.76)	0.64* (0.51-0.81)
ABC (OAS) [25]	1993	Tam	1081	72.8%	82.9%		
		Tam + OFS	1063	73.7%	82.6%	0.95** (0.81-1.12)	0.94** (0.78-1.13)
E3193 [26]	2003	Tam	171	87.9%	95.2%		
		Tam + OFS	174	89.7%	97.6%	0.85** (0.47-1.6)	0.84** (0.37-2.0)
SOFT [27]	2003	Tam	1021	84.7%	95.1%		
		Tam + OFS	1024	86.6%	96.7%	0.83** (0.66-1.04)	0.74** (0.51-1.09)

Abbreviations: CT: chemotherapy; Tam: Tamoxifene; OFS: ovarian function suppression; Exe: exemestane; NR: not reported; DFS: disease free survival; OS: overall survival; HR: hazard ratio. *Compared to no endocrine therapy. **Tamoxifen + OFS compared with tamoxifen alone.

premenopausal patients with early breast cancer if used alone [3, 20, 21]. However, OFS did not significantly improve outcomes if added to adjuvant chemotherapy [22, 23]. For several years, it has been unclear whether OFS provides any additional benefit beyond that offered by adjuvant tamoxifen treatment in premenopausal breast cancer patients who received chemotherapy. Herein, four randomized, double-blind, phase III trials have compared the effect of OFS plus tamoxifen with tamoxifen alone (seen in **Table 1**).

ZIPP trial [24]

The ZIPP (Zoladex in Premenopausal Patients) trial randomized premenopausal women after standard therapy consisting of surgery, radiotherapy and chemotherapy to four groups: goserelin 2 years, tamoxifen 2 years, the combination of both and control group (without tamoxifen or goserelin). At a median follow-up of 12 years, data showed that each type of hormonal therapies was associated with a reduction in the risk of both recurrence and death from breast cancer, but the effect of goserelin depended on whether women received tamoxifen. In women who did not receive tamoxifen, goserelin was associated with a 34% reduction in the risk of DFS and a 29% reduction in risk of overall mortality; while in women who received tamoxifen, there was a much smaller effect, and statistically not significant.

Indeed, there were many obvious limitations in the trial. First, the trial began enrolling patients in 1987 and HR testing was not routinely performed at that time, so the patients enrolled in the trial were regardless of HR status [7, 8]. In fact, about 30% of patients were HR negative in later retrospective testing. Second, the majority of patients in the trial received CMF chemotherapy, including a combination of cyclophosphamide, methotrexate, and fluorouracil or its equivalent, which would be considered insufficient in current practice. Third, chemotherapy and tamoxifen in the trial were administrated concurrently, which was not permitted in clinical practice, because the effect of tamoxifen and chemotherapy is not superior to that of tamoxifen alone or chemotherapy alone. Fourth, quite a part of patients virtually became postmenopausal after receiving chemotherapy, thus for these patients, no additional benefit could be obtained from the administration of OFS.

ABCOAS trial [25]

The Adjuvant Breast Cancer Ovarian Ablation or Suppression (ABCOAS) Trial began enrolling patients in 1993, was a phase III trial to assess the impact of ovarian ablation or suppression to prolonged (5 year) tamoxifen tratment. Patients were assigned to ovarian ablation or suppression (OAS) group (1063) and non-ovarian ablation or suppression (non-OAS) group (1081), respectively. It is a pity that ER status was ignored when patients were enrolled to this trial, and retrospective testing of ER showed that the percentage of ER positive, negative and unknown were 39.1%, 18.2% and 42.7%, respectively. Five-year relapse-free survival (RFS) was 73.7% (95% CI, 70.7% to 76.3%) in OAS group compared with 72.8% (95% CI, 69.8% to 75.5%) in non-OAS group, translating

into an estimated absolute difference of 0.9% (95% CI, -3.1% to 4.9%). Five-year overall survival (OS) was 82.6% (95% CI, 80.0% to 84.9%) in OAS group compared with 80.3% (95% CI, 77.5% to 82.9%) in non-OAS group, for an estimated absolute difference of 2.3% (95% CI, -1.2% to 5.9%). It was concluded that no additional effect of ovarian ablation or suppression was seen on RFS or OS for premenopausal breast cancer without chemotherapy. However, the role of ovarian ablation or suppression in young (< 40 years) women with ER-positive tumors, especially those not receiving chemotherapy, requires further study.

On the basis of the above-reported evidence, in 2011 the American Society of Clinical Oncology (ASCO) experts recommended that ovarian function suppression (OFS) should not be routinely added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy, but they also stated that studies ongoing at that time would have had the potential to alter this recommendation. Since the 2011 ASCO recommendations, the results of two addi-tional phase III studies have been published [26, 27].

E-3193 trial [26]

The Eastern Cooperative Oncology Group conducted a Phase III trial (E-3193) comparing tamoxifen alone (171) with tamoxifen plus OFS (174) in premenopausal women. The trial enrolled a lower-risk cohort of women with a median age of 45 years, and excluded patients in whom chemotherapy was deemed necessary. Almost all the tumors were no more than 2 cm and nodes were negative. Unfortunately, the trial was terminated before reaching the enrollment goal because of slow accrual. The 5-year OS for tamoxifen was 95.2% compared with 97.6% for tamoxifen plus OFS and the adjusted hazard ratio (HR) was 1.19 (95% CI, 0.52 to 2.70). The 5-year DFS rate for tamoxifen was 87.9% compared with 89.7% for tamoxifen plus OFS and the adjusted HR was 1.17 (95% CI, 0.64 to 2.12). It was confirmed that for low recurrence risk patient with node-negative, HR-positive and without chemotherapy, there was no additional benefit of OFS on the basis of adjuvant tamoxifen therapy.

SOFT trial [27]

The Study of Ovarian Function Suppression and Tamoxifen (SOFT) was a large, international trial in which 3066 premenopausal women were randomly assigned to receive 5 years of Tamoxifen (1021), tamoxifen plus OFS (1024), or exemestane plus OFS (1021). It is worth noting that all the patients in this trial were Her2 negative and the criteria for ER positive is no less that 10% of cancer cells are ER stained. The median age was 43 years and 35% of patients were lymph node positive. Over half of patients received adjuvant chemotherapy or neoadjuvant chemotherapy and their median time from surgery to randomization was 8 months, while the remaining patients without receiving chemotherapy were randomized after surgery at a median time from surgery of 2 months. OFS was achieved through administration of the LH-Rha triptorelin in 80.7% of patients and ovary irradiation or removal in the residual patients.

After a median follow-up of 67 months, the estimated DFS at 5 years was 86.6% (95% CI, 84.2% to 88.7%) in the tamoxifen ovarian suppression group and 84.7% (95% CI, 82.2% to 86.9%) in the tamoxifen group, *p* value is 0.10. Most recurrences occurred in patients who had received prior chemotherapy, among whom breast cancer free interal (BCRI) at 5 years was 78.0% in the tamoxifen group and 82.5% in the tamoxifen plus OFS group (hazard ratio for recurrence was 0.78 (95% CI, 0.60 to1.02), and 85.7% in the exemestane plus OFS group (hazard ratio for recurrence was 0.65 (95% CI, 0.49 to 0.87). The authors concluded that adding OFS to tamoxifen did not provide a significant benefit in the overall study population; however, for women at sufficient risk to warrant adjuvant chemotherapy and who remained premenopausal after chemotherapy, the addition of OFS did improve disease outcomes. Furthermore, 233 patients younger than 35 years were included in the primary analysis and 94.0% of them had received prior chemotherapy. Among these women, the 5-year BCRI was 67.7% (95% CI, 57.3 to 76.0) in the tamoxifen alone group, 78.9% (95% CI, 69.8 to 85.5) in the tamoxifen plus OFS.

The meta-analysis showed that, concurrent administration of OFS and adjuvant tamoxifen treatment for premenopausal women with breast cancer has no effect on prolonging DFS and OS, excluding patients who were administered chemotherapy [28]. In fact, the results must be interpreted with caution, because there were indeed some limitations in this

Table 2. Aromatase inhibitor + OFS versus Tamoxifen + OFS

Study	Time of enrolling	Treatment arm	No. of patients	5-years DFS (%)	5-years OS (%)	DFS HR (95% CI)	OS HR (95% CI)
ABCSG-12[29]	1999	Tam + OFS ± Ac Zol	900	NR	NR	1.13 (0.88-1.45)	1.63 (1.05-1.45)
		Ana +OFS ± Ac Zol	903	NR	NR		
SOFT/TEXT[30]	2003	Tam +OFS	2358	87.3%	96.9%	0.72 (0.60-0.85	1.14 (0.86-1.51)
		Exe +OFS	2359	91.1%	95.9%		

Abbreviations: Tam: Tamoxifene; OFS: ovarian function suppression; Ac Zol: zoledronic acid; Ana; Anastrozole; Exe: exemestane; NR: not reported; DFS: disease free survival; OS: overall survival; HR: hazard ratio.

meta-analysis. First, the results of the subgroup analyses were calculated based on the studies with a relatively small sample size. Second, the concomitant anti-cancer treatments used in the four trials were not exactly the same because of advances in chemotherapy. Third, there were differences in the criteria used for determination of menopausal status among the four trials. In addition, the SOFT trial included more patients than any of the rest of the studies, and had a relatively higher impact on the statistical results, which may reduce the reliability of this study.

Concurrent of OFS and aromatase inhibitors

Aromatase inhibitors are proven superior to tamoxifen in postmenopausal breast cancer patients [11-18] and their role in premenopausal women receiving OFS treatment has been partly clarified in the recent years (seen in **Table 2**).

ABCSG-12 trial [29]

Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG-12), is the first trial to investigate the benefit of adjuvant treatment with the combination of goserelin plus either tamoxifen or anastrozole on DFS and OS in premenopausal women with hormone responsive breast cancer. Patients were randomly assigned to goserelin plus either tamoxifen or anastrozole with or without zoledronic acid for 3 years. Early follow-up with median time of 47 months showed that no significant difference on DFS between the anastrozole and tamoxifen group, and a higher rate of distant metastases was observed in anastrozole group than in tamoxifen group. A longer follow-up of 94.2 months confirmed the same result on DFS between two groups (anastrozole, tamoxifen, HR: 1.13; 95% CI 0.88-1.45; P = 0.335), but OS on anastrozole was significantly worse versus the tamoxifen group (HR = 1.63; 95% CI, 1.05-2.52; Cox P = 0.030).

The exploratory analyses provide insight into the potential causes of the surprising OS disadvantage for the anastrozole group. First, ascertainment bias did not affect the collection of data for post-relapse treatment and secondary events because these analyses were not prospectively planned and the data requests were sent to the centers without providing any explanation for the request. Second, once recurrence or metastasis emerged, women receiving initial tamoxifen were more likely to be switched to an aromatase inhibitor than were those in the anastrozole group. For patients in the tamoxifen group, switching to an aromatase inhibitor might have reduced their risk of future recurrence and death. By contrast, patients in the anastrozole group switched to second-line endocrine therapy (not an aromatase inhibitor) seem to have had worse survival outcomes. These two factors might have combined to bias overall survival in favor of the tamoxifen group.

TEXT/SOFT trial [30]

Two randomized, phase III trials, the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), involving premenopausal women with hormone responsive early breast cancer, were initiated in 2003. The two trials were designed to determine the value of adjuvant therapy with the aromatase inhibitor exemestane plus ovarian suppression in premenopausal women. A total of 4717 patients were randomly assigned to the aromatase inhibitor exemestane plus OFS (2359) or tamoxifen plus OFS (2358) for 5 years. Chemotherapy was administered to 57.4% of the study population. At a median follow up of 5.7 years, the 5-year DFS was 91.1% in exemestane plus OFS group and 87.3% in the tamoxifen plus OFS group (HR: 0.72; 95% CI, 0.60-0.85; P < 0.001), and overall survival did not differ significantly between the two groups (HR: 1.14; 95% CI 0.86-1.51; P = 0.37). A recent report found that, SOFT patients at intermediate to high composite risk experi-

enced absolute improvement of 10% to 15%, in 5-year BCFI with exemestane plus OFS versus tamoxifen plus OFS or tamoxifen alone; the benefit of tamoxifen plus OFS versus tamoxifen alone was apparent at the highest composite risk, the no-chemotherapy cohort (for whom composite risk was lowest on average) did well with all endocrine therapies.For TEXT patients, the benefit of exemestane plus OFS versus tamoxifen plus OFS in 5-year BCFI ranged from 5% to 15%; patients not receiving chemotherapy and with lowest composite risk did well with both treatment [31].

The interesting finding was that, for patients who was administrated to adjuvant chemotherapy, 5-year DFS in TEXT trial was 89.8% in exemestane plus OFS group and 84.6% in tamoxifen plus OFS group (HR: 0.69; 95% CI 0.53-0.90; $P < 0.01$); while that in SOFT trial was 84.3% in exemestane plus OFS group and 80.6%% in tamoxifen plus OFS group (HR: 0.84; 95% CI 0.62-1.13; $P > 0.05$). The timing of the initiation of ovarian suppression may explain the difference of DFS for patients who received adjuvant chemotherapy between two trials. In TEXT trial, the average interval was 1.2 months between surgery and the initial use of OFS; While the counterparter was 8 months in SOFT cohort. The longer time from diagnosis to study entry may account for the higher proportion of DFS in this cohort, as compared with the TEXT cohort that received chemotherapy.

Converse results existing between ABCSG-12 trial and TEXT/SOFT trials, we believe the choice of AI does not matter, but greater statistical power in the conjoint analysis of the TEXT/SOFT (with three times the numbers of events of disease recurrence, second invasive cancer, or death in TEXT/SOFT as in the ABCSG-12 trial), the duration of OFS and the basic characteristic of patients do matter. The 3-year duration of aromatase inhibitor therapy in the ABCSG-12 trial may have been insufficient, as compares with 3 years of tamoxifen, which is known to exert a carryover effect after the cessation of treatment.

Indication, duration and adverse effect of OFS

Indication

The question about which population benefit from OFS and endocrine therapy was not answered in previous stud, in which adding ovarian suppression to tamoxifen did not provide a significant benefit on the overall population of premenopausal women [24-28]. However, in the cohort of women who had a sufficient risk of recurrence to warrant adjuvant chemotherapy and remained premenopausal estradiol levels despite of chemotherapy, OFS in addition to tamoxifen reduced the risk of breast-cancer recurrence, as compared with tamoxifen alone [27]. ASCO panel articulated the following recommendations for different cohorts of premenopausal women with ER-positive breast cancers. For women at higher risk of cancer recurrence, because of tumor stage (tumor size, nodal status), grade, or other biologic features, and in whom chemotherapy would ordinarily be advised, the Panel's uniform consensus was to recommend OFS in addition to adjuvant endocrine therapy. However, for the women with lower-risk tumors that were typically stage I with low to intermediate grade and in whom chemotherapy was not necessary, the Panel denied OFS.

Which agent, tamoxifen or an AI, was chosen to administrated with OFS? In ABCSG-12, there was no difference in clinical efficacy between the two groups [28]. In SOFT/TEXT conjoint analysis, recurrence-free survival (RFS) and DFS favored of OFS plus AI over OFS plus tamoxifen [32]. Neither ABCSG-12 nor SOFT/TEXT conjoint analysis demonstrated a survival advantage for AI-based therapy. The ASCO Panel based on these experiences, and recommended that OFS could be administered with either tamoxifen or an AI. But, in SOFT trial, there was a notable trend among women age 35 years and younger favoring OFS plus AI over OFS plus tamoxifen, prompting the Panel to favor of OFS plus AI for higher risk women (such as 4 and more nodes involved or high Ki67 index) and younger women. However, the status of ovarian function may be ambiguity in many situations, including: women with chemotherapy-induced amenorrhea, after hysterectomy, with incomplete ovarian suppression, with incomplete compliance with GnRH agonist treatment, or with other pathophysiological conditions. In such instances, tamoxifen is still the treatment of choice, as it remains effective regardless of ovarian reserve.

Duration

How long was the appropriate duration of OFS for premenopausal breast cancer? In prior tri-

als, different time of duration was used. 2 years of OFS was confirmed as effective as CMF chemotherapy in ZEBRA and IBCSG VIII trial, [20, 21], and in ABCSG5, the combination of goserelin and tamoxifen is statistically significantly better in terms of DFS than CMF chemotherapy and showing a trend towards a survival benefit [32]. The results of ZIPP trial demonstrated an improvement of DFS and OS for patients receiving goserelin in addition to standard treatment [24]. It was not until in NT 01-01 trial that 5 years of OFS was first adopted, and outcomes revealed a significantly reduced HR for recurrence in women who received a combination of goserelin and tamoxifen (HR = 0.73; P < 0.001), and goserelin alone did not achieve a statistically significant risk reduction (HR = 0.93; P = 0.25) [33]. However, standard treatment group with tamoxifen for 5 years was absent in this trial. The SOFT trial showed additional benefit when OFS was administered on certain populations who were at sufficient risk to warrant adjuvant chemotherapy [27]. However, the benefit of survival was not seen in this trial because of the short time of follow up. In addition, we don't know which strategy is better forpremenopasal women with higher risk recurrence: the combination of OFS and tamoxifen/AI or ten years of tamoxifen? The latter was already verified more effective relative to 5 years of tamoxifen. Even so, the SOFT trial was the only trial to confirm the combination of OFS and tamoxifen or an AI was superior to tamoxifen on appropriate population. ASCO Panel recommended 5 years as the suitable duration of treatment, and preferred monthly administration of GnRH agonist therapy.

During the course of OFS by administration of GnRH agonist therapy, clinicians should carefully assess different conditions. If the adverse effects of OFS was tolerable overtime, continue GnRH agonist therapy should be further considered. If intolerable or untreatable, OFS should be discontinued. If the symptoms were marked and arising from OFS, the trade-offs on OFS should be comprehensively considered. In addition, women who receive ovarian suppression should receive monitoring of bone mineral density according to guidelines for postmenopausal women [34, 35].

Adverse effect

The adverse effect of OFS on patient-reported outcomes (PRO) in patients who receives adjuvant tamoxifen was investigated in ZIPP, E-3193 and SOFT trials. Outcomes indicated a greater detrimental effect on menopausal symptoms and sexual activity during treatment with OFS compared with tamoxifen alone. In E-3193, overall QoI was worse when OFS was added to tamoxifen relative to tamoxifen alone at 3 years, with subsequent lessening of differences [26]. In ZIPP trial, the type of endocrine therapy had different effects on patient-reported symptoms only in patients who did not receive chemotherapy, and in patients who received, there was no significant difference on three endocrine therapy groups [24].

In the SOFT trial, Vasomotor symptoms showed the greatest early worsening from baseline. Thereafter, hot flushes improved continuously in patients receiving tamoxifen plus OFS but without reaching baseline scores, whereas scores worsen slightly in patients receiving tamoxifen alone. Patients reported a continuous decline in sexual interest during the whole treatment period, with a clinically meaningful decrease observed between 6 and 60 months in patients on tamoxifen plus OFS and exemestane plus OFS. Changes in gynecologic symptoms were smaller than vasomotor symptoms and marginally clinically meaningful. Bone and joint pain and being troubled by weight gain were clinically worsening over time on both treatment groups [27, 36]. Changes in other symptoms (headache, being irritable, feeling dizzy, appetite feeling sick, tiredness) and global QoL indicators for well-being, mood, and health perception were smaller over time and similar in each treatment group [27].

In the conjoint analysis of SOFT/TEXT trials, global quality of life and the percentages of adverse events of grade 3 or 4 were similar between OFS plus tamoxifen and OFS plus exemetane groups [37]. Women on OFS plus tamoxifen had more hot flashes and night sweats, and that on OFS plus AI therapy had more vaginal dryness, sexual dysfunction, bone and joint pain. Based on previous experiences with tamoxifen and AI therapy in postmenopausal women, it is expected that AI-based therapy would be associated with greater risk of osteoporosis and fractures.

Conclusion

Concurrent administration of OFS and adjuvant tamoxifen treatment for premenopausal wo-

men with HR positive breast cancer has no effect on prolonging DFS and OS. However, patients who were administered with chemotherapy should receive OFS plus endocrine therapy with either tamoxifen or AI. Evidence from TEXT/SOFT trials demonstrated that OFS with the duration of 5 years is reasonable.

Though ASCO panel believed that the data from recent studies of OFS and adjuvant endocrine therapy are practice changing, there is still a long way to go and we are waiting for emerging data to further inform these recommendations. As yet, it is unclear what impact ovarian suppression will have on overall survival. It is well known that ER-positive breast cancer has a long trajectory of recurrence risk. So, long term follow-up of above trials is vital. Tumor with HER2 over-expression is essentially different with that of HER2 normal or hypo-expression, and the anti-HER2 therapy may influence the function of OFS when both therapies were administrated concurrently. Additionally, which type of population may benefit from OFS with tamoxifen or AI therapy is still ambiguous, and more effort must be put to find out factors that predict the likely benefit.

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Disclosure of conflict of interest

None.

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