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นิพนธ์ต้นฉบับ **Original Article**

Results of Primary Prophylaxis G-CSF For in TAC Adjuvant Regimen in Nakhonpathom Hospital

ผลการใช้ G-CSF ป้องกันภาวะเม็ดเลือดขาวต่ำในการรักษาเสริมด้วยยาเคมีบำบัดสูตร TAC ในโรงพยาบาลนครปฐม

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ABSTRACT

Background: TAC is highly effective regimen but has high incidence of febrile neutropenia more than 20%. This study is to review the safety profile of TAC regimen with and without using primary prophylactic G-CSF (PPG)

Patients and methods: From January 2005 - November 2007, thirty patients were received TAC as adjuvant treatment in node positive breast cancer at Nakhonpathom hospital. The patients were divided equally into 2 groups, first group was received TAC regimen as adjuvant chemotherapy without PPG and the second group was received TAC regimen as adjuvant chemotherapy with PPG. Age, size of tumor, lymph node involvement, doses received and toxicities were recorded.

Results: The using of G-CSF from the first cycle (PPG) reduced the incidence of neutropenia in patients treated with TAC (46.67% vs. 2.22%) and reduced the incidence of febrile neutropenia in patients treated with TAC (6.67% vs. 0%). PPG also improved the compliance of TAC regimen. The percentage of patients who did not delayed receiving TAC increased from 91.11% to 97.77% in the patients who received PPG.

Conclusions: This review shows that PPG reduces the incidence of neutropenia, neutropenic fever and improved the compliance of adjuvant TAC regimen. TAC is highly effective adjuvant treatment and

with G-CSF support, has acceptable safety profile.

Keywords: G-CSF, primary prophylaxis, adjuvant chemotherapy, TAC

บทคัดย่อ

TAC เป็นชุดยาที่ใช้ในการรักษาเสริมในมะเร็งเต้านมที่ได้ผลดีมากแต่มีอุบัติการณ์การเกิดภาวะเม็ดเลือดขาวต่ำมากกว่า 20% การศึกษานี้เป็นการเปรียบเทียบผลทางด้านความปลอดภัยระหว่างการใช้ และไม่ใช้ G-CSF เพื่อป้องกันการเกิดภาวะเม็ดเลือดขาวต่ำ

ตั้งแต่ มกราคม 2548 ถึง พฤศจิกายน 2550 ผู้ป่วยมะเร็งเต้านมที่มีการแพร่กระจายไปต่อมน้ำเหลืองจำนวน 30 คน ในโรงพยาบาลนครปฐมได้รับการรักษาเสริมด้วยยาเคมีบำบัดสูตร TAC โดยผู้ป่วยกลุ่มที่ 1 ไม่ได้รับ G-CSF ส่วนกลุ่มที่ 2 ได้รับ G-CSF (กลุ่มละ 15 ราย) เพื่อป้องกันการเกิดภาวะเม็ดเลือดขาวต่ำ

พบว่าการใช้ G-CSF ช่วยลดอุบัติการณ์การเกิดภาวะเม็ดเลือดขาวต่ำ (46.67% กับ 2.22%) และช่วยลดอุบัติการณ์การเกิดไข้และเม็ดเลือดขาวต่ำลง (6.67% กับ 0%) นอกจากนี้การใช้ G-CSF ยังช่วยเพิ่มอัตราการให้ยาเคมีบำบัดโดยไม่ต้องเลื่อนเวลาการให้ออกไปจาก 91.11% เป็น 97.77% ในกลุ่มที่ใช้ G-CSF ป้องกัน

จากผลการศึกษานี้แสดงให้เห็นว่าการใช้ G-CSF ป้องกันช่วยลดอุบัติการณ์การเกิดภาวะเม็ดเลือดขาวต่ำในการรักษาเสริมด้วยยาเคมีบำบัดสูตร TAC และยังช่วยให้สามารถให้ยาเคมีบำบัดแบบการรักษาเสริมได้ตรงเวลา

คำสำคัญ: จี-ซีเอสเอฟ ป้องกันภาวะเม็ดเลือดขาวต่ำ, การรักษาเสริมด้วยเคมีบำบัด

Introduction

In the late 1970s and 1980s, anthracycline-containing regimens were tested in adjuvant trials and were demonstrated to be slightly but significantly superior to CMF-like regimens[1]. Docetaxel-containing regimens have shown superiority over standard regimens in metastatic breast cancer[2]. More recently, a randomized phase III trial by the Breast Cancer International Research Group (BCIRG 001) has shown that the combination of docetaxel, doxorubicin and cyclophosphamide (the TAC regimen) is superior to FAC as adjuvant chemotherapy for node-positive operable breast cancer[3,7] by reducing the risk of recurrence at 28% and reducing the risk of death at 30%. TAC regimen can be one of the new standards of care for these patients[4]. Unfortunately, TAC was clearly more toxic than FAC, not only with neutropenic fever events (24.7% versus 2.5%, p = 0.001)[3], but also with many nonhaematological side-effects like asthenia, stomatitis, diarrhea, myalgia and others. In 1998, the Spanish Breast Cancer Research Group (GEICAM, Grupo Español de Investigación en Cáncer de Mama) started the study GEICAM 9805, a phase III trial comparing the TAC regimen with FAC as adjuvant chemotherapy for high-risk, node-negative breast cancer[5] and their conclusion was primary prophylactic G-CSF (PPG) reduced the incidence of neutropenic fever and other clinically relevant events (grade 2 or greater anemia, asthenia, anorexia, myalgia, nail disorders and stomatitis) associated with TAC chemotherapy [6].

Patient and methods

From January 2005 - November 2007, thirty patients with node positive breast cancer were received TAC as adjuvant treatment in Nakhonpathom hospital. The patients were divided equally into 2 groups, first group was received TAC as adjuvant treatment without PPG and second group was received TAC adjuvant with PPG. Age, size of tumor, lymph node involvement, doses received and toxicities were recorded.

Chemotherapy regimen (TAC) was docetaxel 75 mg/m^2 i.v. day 1, doxorubicin 50 mg/m^2 i.v. day 1, cyclophosphamide 500 mg/m^2 i.v. day 1, every 3 weeks for six cycles.

Patients received premedication with dexamethasone (six doses of 8 mg p.o., starting the night before chemotherapy and ending the evening of the day after chemotherapy) in order to prevent fluid retention. Antiemetic treatments were by corticoids and selective 5-HT3 receptor antagonist in both groups.

Primary prophylactic antibiotic therapy (ciprofloxacin 500 mg b.i.d. on days 5-14 of each cycle) was mandatory using during the first chemotherapy course and subsequent cycles for patients in both groups.

The G-CSF regimen consisted of 1 vial of filgastrim (300 μg/day) subcutaneously, administered on days 4-10 after chemotherapy.

A complete blood cell count was mandatory on days 7 and 21 of each cycle. Toxicity was graded by using the NCI-CTC version 1.0.

Results

Patients' characteristics (table 1).

Average age of the patients was 45.5 (41-60) years. Average size of tumor was 4.5 cm. Average numbers lymph node removed were 18.5 (12-25) nodes and average numbers of positive lymph node were 2.5 (1-10) nodes.

Table 1 Patients Characteristic (overall)

Mean age (range) (years)	47.65 (41-57)
Mean BSA (m^2)	1.513
Mean size of tumor (cm)	4.1
Staging by size (number of patient)	
T1	1
T2	16
T3	3
T4	0
Number of lymph node (range)	18.95 (15-25)
Number of positive lymph node (range)	2.4 (1-7)
Node positive patient	
Positive 1-3	18
Positive 4	2

All of the patients received mastectomy. 55% of the patients were postmenopausal and hormonal receptors were positive in 60% of patients.

In without PPG group, median total dose of docetaxel was 448.66 mg, median total dose of doxorubicin was 299.33 mg and median total dose of cyclophosphamide was 2,993.33 mg.

In with PPG group, median total dose of docetaxel was 450 mg, median total dose of doxorubicin was 300 mg and median total dose of cyclophosphamide was 3,000 mg. (table 2).

Table 2 Patients Characteristic

Numbers of cycles	6	
Menopause (%)	55	
ER + and/or PR + (%)	60	
Mastectomy	20 (100%)	
Median total dose (mg/m^2)	without prophylaxis	with prophylaxis
Docetaxel	448.66	450
Doxorubicin	299.33	300
Cyclophosphamide	2,993.33	3,000

Treatment exposure

All of the patients received complete 6 cycles of adjuvant TAC. Dose delayed were found 8.88% in group without PPG and 2.22% in PPG group. Dose reductions were found 2.22% in group without PPG only in table 3. Causes of dose delayed in group without PPG were hematological toxicity in 7.77% and other in 1.11%. Causes of dose delayed are shown in table 4 and other grade 3, 4 toxicities are shown in table 5.

There was neutropenia in group without PPG in 46.67% and febrile neutropenia was found in 6.67%. In PPG group, neutropenia was found in 2.22% and no febrile neutropenia in this group. No septic death was found in both groups (table 6).

Discussions

From ASCO meeting 2002, TAC regimen was shown superiority to FAC in adjuvant treatment of node positive breast cancer[7] and was confirmed by final result of BCIRG001 that combination of docetaxel, doxorubicin and cyclophosphamide (the TAC regimen) is superior to FAC as adjuvant che-motherapy for node-positive operable breast cancer by reducing the risk of recurrence at 28% and reducing the risk of death by 30%[4,8] but TAC regimen has higher side effect such as neutropenia and febrile neutropenia[9]. GEICAM 9805 study showed that PPG reduced the

Table 3 Treatment exposure

	without prophylaxis	with prophylaxis
Patients complete 6 cycles	100%	100%
Numbers of cycles (total)	90	90
Cycles without dose delayed	82 (91.1%)	88 (97.77%)
Dose delayed	8 (8.88%)	2 (2.22%)
4-7 days	6 (6.66%)	2 (2.22%)
> 7 days	2 (2.22%)	0
Dose reduction	2 (2.22%)	0

Table 4 Causes of dose delayed

	without prophylaxis	with prophylaxis
Hematologic toxicity	7 (7.77%)	1 (1.11%)
Nonhematologic toxicity	0	1 (1.11%)
Other	1 (1.11%)	0

Table 5 Grade 3-4 Toxicity

Nausea	2 (10%)
Vomiting	2 (6.67%)
Asthenia	4 (20%)
Stomatitis	0
Anemia	2 (6.67%)
Thrombocytopenia	2 (6.67%)

Table 6 Grade 3-4 Toxicity (neutropenia and death)

	without prophylaxis	with prophylaxis
Neutropenia	7 (46.67%)	2 (2.22%)
Febrile neutropenia	1 (6.67%)	0
Death	0	0

incidence of neutropenic fever and other clinically relevant events (grade 2 or greater anemia, asthenia, anorexia, myalgia, nail disorders and stomatitis) associated with TAC chemotherapy[6].

In this review, using of G-CSF from the first cycle (PPG) reduced the incidence of neutropenia in patients treated with TAC (46.67% vs. 2.22%) and reduced the incidence of febrile neutropenia in patients treated with TAC (6.67% vs. 0 %) these are the same results that found in GEICAM 9805 study. Avoiding neutropenic fever events and the associated risk of life-threatening infections, are importance in the adjuvant setting, where many patients can be already cured by local treatment itself. Although the mortality of neutropenic fever is very low today, some toxic deaths due to neutropenic sepsis in breast cancer patients treated with doxorubicin plus docetaxel have recently been reported[10].

PPG also improved the compliance with TAC. The percentage of patients who did not delayed received TAC increased from 91.11% to 97.77% by using PPG.

Conclusions

This review shows that PPG reduces the incidence of neutropenia, neutropenic fever and improved the compliance of adjuvant TAC regimen.

TAC is highly effective adjuvant treatment and with G-CSF support, has acceptable safety profile.

References

1. Early breast cancer trialists' collaborative group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet. 2005;365:1687-717.
2. Nabholtz JM, Falkson C, Campos D, et al. Docetaxel and doxorubicin Compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol. 2003;21(6):968-75.
3. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005;352:2302-13.
4. Perez E. TAC-A new standard in adjuvant therapy for breast cancer?. N Engl J Med. 2005;352: 2346-8.
5. Goldhirsch A, Glick JH, Gelber RD, et al. Meeting highlights: International consensus panel on the treatment of primary breast cancer. J Natl Cancer Inst. 1998;90:1601-8.
6. Martin M, Lluch A, Segui MA, et al. Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC): impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen. Ann Oncol. 2006;17(8):1181-3.
7. Nabholtz JM. Phase III trial comparing TAC with FAC in the Adjuvant Treatment of Node-Positive Breast Cancer Patients. 38th Annaul Meeting of the American Society of Clinical Oncology(ASCO), May 18-21, 2002 Abstract 141.
8. Martin M. Docetaxel-based regimen (TAC) improves DFS and OS over FAC in node-positive breast cancer patients: Efficacy, safety and quality

of life at 55 months follow up. 4th European Breast Cancer Conference(EBCC), 2004.

9. Martin M. Hematologic toxicity of BCIRG001. San Antonio Breast Cancer Symposium 2003. Abstract 43.
10. Brain EG, Bachelot T, Serin D, et al. Life-threatening sepsis associated with adjuvant doxorubicin plus docetaxel for intermediate-risk breast cancer. JAMA. 2005;293:2367-71.