評估乳癌病患使用 G-CSF 預防化學治療期間嗜中性白血球低下及併發性發燒之研究

Study on the Use of G-CSF in Breast Cancer Patients for Managing Chemotherapy-induced Febrile Neutropenia

中文摘要

動機 嗜中性白血球低下合併發燒 (FN) 是病患在接受癌症化療時產生的嚴重血液副作用，臨床上可使用抗生素或顆粒性白血球群落刺激因子(G-CSF)來預防。G-CSF 爲細胞激素 (造血生長刺激因子)，它能調節造血幹細胞的增殖，分化和功能，並呈現劑量依賴性的增加血液循環中嗜中性白血球之數量。在早期的臨床試驗中顯示，於小細胞肺癌病患中，以 G-CSF 來做初級預防性治療可縮短化療引起嗜中性白血球低下的時間，並進一步降低 FN、感染、住院及使用抗生素約 50 %之發生率。在此研究中，G-CSF 自化療後第四天開始給予直到第十七天，FN 之發生率從 77%降到 40%。而另一個針對乳癌病患的研究中，在經過化療後第四天至第十天的 G-CSF 給予後，對於接受 TAC (adriamycin, paclitaxel, 及 cyclophosphamide)化療的病患，可使 FN 的發生率從 27.5%降至 7.5%。根據目前臨床準則的建議，G-CSF 只適用於 FN 風險大於 20%的病患 。

目的 G-CSF 屬於高價位的藥品，目前在辜公亮和信治癌中心，G-CSF 由於健保局的規範下通常開予三天的處方。本研究的主要目標爲研究在乳癌病患在接受 G-CSF 初級及次級預防後其 FN 的發生率；次要目標爲探討 G-CSF 的處方型態和評估在目前健保的給付規範下 G-CSF 使用的成本效益分析。

研究設計 本研究爲病歷回溯性研究，納入 2007 年於和信治癌中心接受化學治療或 lenograstim 的乳癌病患。收集的資料包括了病人的年紀、性別、腫瘤類型、化療處方及劑量、G-CSF 使用劑量及期間、住院時間及成本等。接著，依照病患接受的化療處方其 FN 之風險分成三組，分別爲高(>20%)、中(10-20%)、低(<10%)，以找出在不同組之 FN 風險及其 G-CSF 使用的型態。此外，我們進一步著重在研究乳癌病患接受化療處方 TAC, ATC 和 CAF 其使用 G-CSF 的型態及 FN 之發生率，並和目前文獻研究的結果加以比較以評估臨床療效及延長或增加 G-CSF 使用時間所相對的成本效益分析。最後，以健保給付者的立場來建構決策分析模型並進行成本效益分析，成本僅考量直接醫療成本，而降低 FN 風險所相關的結果及參數則是參考文獻及和信的資料而得。

結果 自 2007 年 1 月至 2007 年 12 月， 共有 511 位於和信治癌中心接受化療和 lenograstim 之乳癌病患納入本研究。 在這些患者中，接受高 FN 風險化療之病

人在經過三天之 G-CSF 給予後（5 μg/kg/day）並沒有因爲接受 G-CSF 預防性治療而明顯降低 FN 之發生率（33.33%）。此外，經過資料分析後，我們發現在乳癌病患最常給予的化療處方爲(1) adriamycin, paclitaxel, 及 cyclophosphamide 序貫療法(ATC); (2) adriamycin, paclitaxel, 及 cyclophosphamide 合併療法(TAC); 和(3) cyclophosphamide, adriamycin, 及 5-fluorouracil (CAF)。在這三組接受化療及 G-CSF 之病患中，TAC 發生 FN 之風險(33.33 %，初級預防)最爲顯著，明顯的比 ATC (6.66%，初級預防)及 CAF(5.97%，次級預防)二組高出許多。而 G-CSF 使用的期間則分別爲：CAF 組－3.19 天、ATC 組－6.08 天、TAC 組－2.95 天。最後，在接受不同化療處方的三組中，由於健保局的規範，大部分病人僅接受三天的 G-CSF 治療。經過成本效益的分析後，將三天之 G-CSF 療程比上七天之 G-CSF 療程(文獻)其增加成本效益比(ICER)明顯爲高(每避免一次 FN 需多支出 120,265 元)。

討論 在乳癌病患中，接受較高 FN 風險之化療及 G-CSF 的病患，仍有很高的比率會發生 FN，這可能和 G-CSF 使用的時間有關，我們發現接受 TAC 化療的病患即使給予 G-CSF 的預防性治療，其發生低嗜中性白血球合併發燒之機率仍遠比臨床試驗所得到之數據大約高出五倍(33.33% vs.7.5%)。此外，在健保的規範之下，臨床上使用 G-CSF 的天數也遠低於準則中之建議(3 天 vs.10~14 天)。在 ATC 組中(6.66%)，和 Citron 等人之研究(2%)相比，FN 之發生率約高出三倍。而 CAF 組所發生 FN 之比率在早期的研究中(2~5%)及本研究(5.97%)則是相似的。在 TAC 組中 FN 發生率明顯較高，其確切原因仍是未知，但可能和使用較短期間(3 天)之 G-CSF 有密切的關係。

結論 根據本研究的結果，在接受高風險化療處方的病患，即使接受了 G-CSF 的預防性治療，但仍有很高的比例會發生低嗜中性球合併發燒。這可能是由於在目前健保給付規範下，G-CSF 只能使用 3 天的療程。此外，許多病患在接受完 3 天的療程後，仍需再接收另一次的 3 天療程以治療嗜中性白血球低下。在經過成本效益分析後，初步的結果顯示七天的 G-CSF 療程不只是有好的成本效益，在臨床使用上也可達到相當程度的成本節省。因此，進一步進行前瞻性研究來找出 G-CSF 最適當的使用天數爲本研究之未來方向，並希望以本研究的結果來說服健保局以評估修正 G-CSF 給付規範之可能性。

英文摘要

Rationale Febrile neutropenia (FN) is a serious hematological toxicity of cancer chemotherapy and could be prevented with the prophylactic use of antibiotics and/or granulocyte colony-stimulating factor (G-CSF). G-CSF is hematopoietic growth-stimulating factor, which regulates the proliferation, differentiation and function of hematopoietic cells. G-CSF dose-dependently increases the cell number of circulating neutrophils. Early clinical trials indicated that primary prophylaxis with G-CSF reduces the duration of chemotherapy-induced neutropenia resulting in a 50%

reduction in FN, infections, hospitalization, and the use of antibiotics in small cell lung cancer patients. In the study, the rate of FN was reduced from 77% to 40%, with long-term G-CSF treatment started on day 4 and continuing through day 17. Regarding to breast cancer patients, G-CSF as primary prophylaxis administered on days 4 to10 after TAC (adriamycin, paclitaxel, and cyclophosphamide) chemotherapy regimen lead to a reduction of FN risk from 27.5% to 7.5%. Based on the practice guidelines, primary prophylaxis of G-CSF treatment protocol can only be used for high risk patients with FN.

Objective G-CSF is relatively expensive medicine. Currently, at the Sun Yat-Sen Cancer Center (SYSCC), G-CSF was prescribed to patients with prior severe neutropenia or FN for only three days due to the regulation of national health insurance (NHI). The main objective of this study was to investigate the rate of FN after primary and secondary prophylaxis of G-CSF in breast cancer patients (n=511); the secondary objectives were to investigate the prescribing pattern of G-CSF at SYSCC and to evaluate the cost-effectiveness of G-CSF use under the regulation of NHI.

Study Design We performed a retrospective chart review of breast cancer patients who received chemotherapy or lenograstim at SYSCC during year 2007. The information included in this review were patients' age, sex, tumor type, dosage of chemotherapy, the dose and duration of G-CSF, history of FN and neutropenia, and the length and cost of hospitalization due to FN. Then, we divided patients into three groups according to the risk of FN on received chemotherapy regimen, high (>20%), intermediate (10-20%), low (<10%), to find out the FN risk in different groups and also the regimen of lenograstim use. Furthermore, we focus on the FN risk and regimen of G-CSF use in patients with breast cancer who received chemotherapy regimen of TAC, ATC, and CAF. All these data will be analyzed and compared with the current literature to evaluate the efficacy and cost-effectiveness of G-CSF. Finally, a decision-analysis model was constructed from a health insurer's perspective to evaluate the cost-effectiveness by considering direct medical costs only. The data required for the decision-analysis model were obtained from the medical literature and data from SYSCC.

Results Between January 2007 and December 2007, 511 breast patients who received both chemotherapy and lenograstim at SYSCC were enrolled in the study. Patients in the high risk group (TAC) did not have significantly reduced rate of FN (33.33%) after receiving lenograstim treatment for 3 days. Furthermore, the three common

chemotherapy regimens for the treatment of breast cancer were (i) sequential treatment with doxorubicin, paclitaxel, and cyclophosphamide (ATC), (ii) combined treatment with doxorubicin, docetaxel, and cyclophosphamide (TAC), and (iii) treatment with cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF). Comparison of three treatment groups, group TAC (33.33%, with primary prophylaxis G-CSF) was associated with higher FN incidence than ATC (6.66%, with primary prophylaxis G-CSF) and CAF (5.97%, with secondary prophylaxis G-CSF) groups after 3 days lenograstim treatment. And the duration of lenograstim were 3.19 days in CAF group, 6.08 days in ATC group, and 2.95 days in TAC group, respectively. Finally, most of patients in the TAC and CAF groups received only 3 days of G-CSF prophylaxis due to the regulation of national health insurance (NHI). After the cost-effectiveness analysis, the incremental cost-effectiveness ratio (ICER) in comparison of 7-day treatment regimen (according to clinical trials) versus 3-day treatment regimen was unacceptably high (N.T.120,265 per FN episode avoided).

Discussion The higher FN incidence in breast cancer patients of high risk chemotherapy regimen after G-CSF prophylaxis may be due to the short duration of G-CSF use. The risks of FN in TAC group of SYSCC and the prior study were 33.33% and 7.5%, respectively. This 5-fold higher risk in the TAC group may be due to the difference in period of G-CSF prophylaxis reducing from 7 days to 3 days in the SYSCC. In ATC group, the risk of FN in the present study (6.66%) was 3 times higher than the report of Citron et al. (2%). Earlier studies indicate the risk of developing FN in patients received CAF chemotherapy are ranging from 2 to 5 % while in the present study the risk was similar (5.97%). The reason of unexpected higher incidence of FN in TAC regimen is unclear, but is highly likely that the decreased efficacy was due to short time period (3 days) of G-CSF treatment.

Concluding Remark Based on present results, patients who received chemotherapy of high risk in FN and G-CSF for primary prophylaxis still had the rate of FN 33.33%. The result may be due to the 3-day G-CSF use under the regulation of NHI. Moreover, many patients under 3-day G-CSF regimen may further require another 3-day G-CSF regimen to support the developed neutropenia. Additionally, the cost-effectiveness model provides evidence that 7-day G-CSF regimen is not only cost-effective but also cost-saving in clinical settings. There appeared to be both clinical and economic benefits from prophylaxis with standard administration (7-day) of G-CSF. Therefore, further prospective study should be performed to find out the most appropriate duration of G-SCF use. The result could be provided as an evidence to persuade and modify the reimbursement policy of NHI.