Indonesian Journal of Cancer Chemoprevention, October 2012
ISSN: 2088–0197
e-ISSN: 2355-8989

Cost Analysis of Cancer Side Effects Therapy in Cancer Patients in Rumah Sakit Prof. Dr. Margono Soekarjo Purwokerto

Febrian Pradana, Tunggul Adi Purwonugroho, Heny Ekowati*

Pharmacy Department, Faculty of Medicine and Health Sciences, Universitas Jenderal Soedirman, Jalan Dr. Soeparno, Karangwangkal, Purwokerto 53123

Abstract

Cancer is the leading cause of death in Indonesia. Generally, cancer therapy use chemotherapy, radiation, surgery or combination of those. Various side effects caused by cancer therapy make the use of additional drugs. This leads to an increase in total cost incurred to cancer patients. The purpose of this study was to describe the treatment of cancer therapy's side effects as well as the average cost of side effects treatment, and its percentage in the total cost of cancer patients in Rumah Sakit Margono Soekarjo. This research was a descriptive study with retrospective data by total sampling method obtained from patients' medical and receipts records of five most common cancers (breast, nasopharynx, Non Hodgkins Lhympoma (NHL), ovarian, and cervix) during January-December 2010. The average cost of patient's side effects treatment was calculated by the average cost of side effects compared to the average total direct costs incurred to cancer patients. The samples was obtained from the population of 2261 patients who met the inclusion criteria, that are 73 patients consist of 62 female patients and 11 male patients. The most common side effects of cancer therapy were nausea and vomiting (59.80%), nausea-vomiting, anemia, and pain (16.44%), and nausea-vomiting and anemia (15.07%). The most used therapy was vitamin B complex followed by histamine-2 inhibitor. The average cost of side effects for breast cancer was Rp 1,715,373 (8.73%), nasopharynx was Rp 1,149,049 (6.98 %); NHL was Rp 360,778 (1.97 %); ovary was Rp 911,118 (3.61 %) and cervical was Rp 1,416,027 (8.87 %). The results indicated that the hospital needs to pay more attention on nausea-vomiting effect of chemotherapy, and also cervical cancer side effects therapy as the most costly.

Keywords: Cost Analysis, Cancer, Side Effects, Prof. Dr. Margono Soekarjo Hospital

INTRODUCTION

Cancer is a disease characterized with uncontrolled cells differentiation and proliferation. It causes cells continuing to grow, to spread abnormally, and to invade other normal cells, causing metabolic disorders and may lead to death if the cancer was not cured (Katzung, 2007). There are various therapies that can be done to treat cancer. Surgery, radiotherapy, chemotherapy, or combination of them, are widely used to treat cancer. Nevertheless, cancer therapy's side effects are well known to cause clinical and economical burden (Anonymous, 2009; WHO, 2005).

Cancer therapy side effects can reduce patients' quality of life. Moreover, there is also economic effect because of it. Additional drugs are required to treat chemotherapy side effects, thus there will be increase of total cost spent by either cancer patients or other payers, such as insurance (Balmer *et al.*, 2005). The number of cancer patients in Rumah Sakit Prof. Dr. Margono Soekarjo (RSMS) in 2010 is about 3369 patients.

Cancer rate is followed by the incidence of side effects of therapy. There are many side effects that frequently occur, such as nausea, vomiting, and anemia. Nausea is defined as the feeling of wanting to vomit or craving symptoms experienced around the throat and stomach, indicating that the patient will soon vomit.

*Corresponding author e-mail: heny240377@gmail.com

Vomiting is defined as the expulsion of gastric contents, which sometimes requires a strong boost (Garret *et al*., 2003). Nausea and vomiting can be either acute, delayed, or anticipatory. The stimulation of central vomiting and chemoreceptor trigger zone by chemotherapy can induce nausea. Chemotherapy also causes enterochromaffin cell damage, thus serotonin release occurs to stimulate chemreceptor trigger zone to induce nausea. The example of chemotherapeutic agents that induce nausea and vomiting are alkylating agents (Dipiro *et al.*, 2005)

Anemia is a myelosuppressive effect. Myelosuppressive is the decrease of bone marrow efficiency/capacity to produce blood cells. It can be caused by cancer therapy. Chemotherapeutic agents kill functional cells that are in charge if producing blood cells, such as erythrocyte, leukocyte, thrombocytes, and others. So the amounts of those cells in the body were decreased (Amy, 2009). Anemia is a symptom characterized by low hemoglobin level, which is usually less than 10 g/dl (WHO, 2006). It can be caused by the depression of bone marrow or by nephrotoxicity of chemotherapeutic agent inducing the decrease of erythropoietin production. Cisplatin is one alkylating agent which has nephrotoxicity as the side effect (Rodgers, 2008). Other side effects of cancer therapy are mucositis, alopecia, cardiotoxicity, and suffering pain (NCI, 2012).

The purpose of this study was to describe the treatment of side-effects from cancer therapy as well as the average cost of them, together with the percentage of cancer patients in Margono Soekarjo Hospital. The results of this study can be referred as an advice for hospital management to choice effective therapy for cancer side effects treatment.

MATERIALS AND METHODS

Study Design

The study was a descriptive study with retrospective data by total sampling method obtained from patients' medical and receipts records of five most common cancers [breast, nasopharynx, Non Hodgkins Lhympoma (NHL), ovarian, and cervical] in Rumah Sakit Prof. Dr. Margono Soekarjo (RSMS) during January-December 2010. The study was conducted on April-July 2012.

Study Subjects

The total of 2261 patients of top 5 cancers patients were selected by inclusion criteria. The inclusion criteria were patients with diagnosis of cancer, either with or without comorbidities and having documentation of therapy's side effect, patients with complete medical and receipts records, and patients who have completed 6 chemotherapy cycles. The inclusion criteria selected 73 patients from those 2261, and total sampling method was used to all the 73 patients to be the subjects of the study. Data were collected from medical and receipts office in Rumah Sakit Margono Soekarjo Purwokerto.

Data Collection

Data collection was done by using data collection sheet. Data collection sheet was used to record data from medical and receipts records. Medical data recorded were medical record number, gender, age, diagnose, therapy documentation, side effects documentation, laboratory data, and status of cancer. Receipts data recorded were the detailed therapy cost and total cost spent by cancer patients.

Data Analysis

Data from medical record were analyzed and described based on the types and the therapy of cancer therapy's side effects. That data also described the pattern of cancer and cancer treatment's side effect therapy. Data from receipts records were analyzed and components of the cost of therapy side effects incurred to the patients during treatment were compared to the overall total direct cost. The average percentage of the cost of the side effects treatments was determined by the average cost of side effects treatments compared to the average total direct costs incurred to cancer patients.

RESULTS AND DISCUSSION

The number of samples obtained was 73 patients, consisting 62 female patients and 11 male patients, who met the inclusion criteria among a total population of 2261 patients. Among them, there were 39 breast cancer patients, 8 nasopharyngeal cancer patients, 14 NHL cancer patients, 7 ovarian cancer patients, and 5 cervical cancer patients. A total of 66 patients had no comorbidities disease. Mostly used treatment in cancer patients was

chemotherapy (57,53%), followed by a combination of chemotherapy and surgery (Table I). The group widely used for chemotherapy was combination of alkylating agent, anticancer antibiotics, and antimetabolite. The most common type of cancer treatment side effect was nausea-vomiting (58,90%), and followed by combination of nausea-vomiting, anemia, and pain suffering (Table II). The percentage of side effects treatments cost compared to the total direct costs grouped based on type of cancer showed that cervical cancer had the highest percentage (8,87%) (Table III).

Then the percentage of side effects treatments cost compared to the total direct costs of each type of therapy showed that radiation therapy had the highest percentage (12,09%) (Table IV). Mostly used therapy was vitamin B complex followed by histamine-2 inhibitor (Table V).

Table I. Distribution of the number of cancer patients based on treatment patterns in RSMS

	Cancer type					Total	Percentage (%)
	Breast	Nasopharinx	NHL	Ovarian	Cervical		
Chemotherapy	32	-	10	-		42	57.53%
Radiation	1	-	-	-	1	2	2.74%
Chemotherapy and surgery	6	2	4	7	-	19	26.03%
Chemotherapy and radiation	-	-	-	-	2	2	2.74%
Chemotherapy, radiation, and surgery	-	6	-	-	2	8	10.96%
		Total				73	100%

Table II. Distribution of the cases of cancer therapy side effects in RSMS

Types of side effects of therapy	Number of patients						Percentage (%)
	Breast	Nasopharinx	NHL	Ovarian	Cervical	Total	
Nausea-vomiting	29	1	1	1	1	42	58.90
Nausea-vomiting+bleeding	3	-	-	-	-	3	4.11
Nausea-vomiting + anemia	4	2	3	1	1	11	15.07
Anemia+bleeding+nausea-vomiting	1	-	-	-	-	1	1.37
Nausea-vomiting+anemia+pain	2	4	-	5	1	12	16.44
Anemia +pain+bleeding	-	-	-	-	1	1	1.37
pain+bleeding+nausea-vomiting+anemia	-	-	-	-	1	1	1.37
Anemia+bleeding+pain+ nausea-vomiting+neutropenia	-	1	-	-	-	1	1.37
		Total				73	100%

Table III. The percentage of side effects treatments cost compared to the total direct costs for five top cancer patients in RSMS

Type of cancer	Average of direct cost (IDR)	Average of side effect therapy cost (IDR)	Side effect therapy cost compared to average of direct cost (%)
Breast	19,633,621	1,715,373	8.73%
Nasopharinx	16,455,038	1,149,049	6.98%
NHL	18,283,619	360,778	1.97%
Ovarian	25,224,706	911,118	3.61%
Cervical	15,970,903	1,416,027	8.87%

Table IV. The percentage of side effects treatments cost compared to the total direct costs grouped by cancer treatment types in RSMS

Type of cancer	Average of direct cost (IDR)	Average of side effect therapy cost (IDR)	Side effect therapy cost compared to average of direct cost (%)
Chemotherapy	18,849,096	1,425,718	7.56
Radiation	12,815,304	1,548,808	12.09
Chemotherapy and surgery	21,563,158	1,011,593	4.69
Chemotherapy and radiotherapy	11,713,436	651,404	5.56
Chemoptherapy, radiation, and surgery	19,916,268	1,387,201	6.97

Table V. Drug characteristics and cost used in cancer therapy side effects treatments in RSMS

Group of therapy	Number of patients						Total cost (in IDR)
	Breast	Nasopharinx	NHL	Ovarian	Cervical	Total	
a. Serotonin antagonist							
-Ondansetron	28	5	4	5	2	42	1,767,960
-Troposetron	-	4	-	2	1	7	1,203,125
b. Dopamine antagonist							
- Metoclopramid	8	8	13	7	4	40	3,089,020
- Domperidone	-	1	1	-	-	2	20,095
c. Antacid	-	3	13	3	1	20	64,984
d. Histamine antagonist							
- Ranitidin	30	6	14	5	5	60	1,732,406
- Cimetidine	-	-	-	1	1	2	15,400
e. Corticosteroid							
-Dexamethasone	8	3	3	1	2	17	140,789
-Methylprednisolone	1	6	3	3	1	14	1,261,192
-Kalmethasone	1	-	-	2	-	3	61,256
f. Vitamin b complex	39	5	13	6	5	68	97,794
g. Blood transfusion	9	7	4	6	4	30	23,550,000
h. Ferrous sulfate	2	4	0	5	5	16	17,195
i. Vitamin K	0	2	1	4	0	7	24,788
j. Tranexamic acid	-	4	3	3	5	15	954,844
k. Carbazochrome	-	3	-	1	2	6	1,250,708
l. Analgesic							
-Mefenamic acid	8	5	6	7	-	26	56,868
-Ibuprofen	1	2	2	2	-	7	112,406
-Ketorolac	2	2	2	6	1	13	564,859
-Tramadol	-	3	1	-	-	4	134,736
-Kalium diclofenac	-	3	-	-	-	3	26,550
-Methampyrone	-	2	-	-	-	1	11,638
-Natrium diclofenac	-	2	-	-	-	2	6,700
-Piroxicam	-	1	-	-	-	1	3,188
-Meloxicam	-	-	-	-	1	1	18,723
-Ketoprofen	-	1	-	1	1	3	63,869
-Paracetamol	-	4	4	-	2	10	19,003
-Meperidine	-	-	-	1	-	1	14,990

*G- CSF : *Granulocyte colony stimulating factor*

This study showed there were 66 cancer patients with no comorbidities disease diagnose and 7 patients with cancer and comorbidities disease. Comorbidities disease suffered by all patients included was anemia. Medical reports report anemia as the side effects of cancer therapy.

Results showed that cancer patients were given various therapies depending on the type and severity of cancer**.** It was observed that the most widely used treatment in cancer therapy was chemotherapy. In cancer patients, chemotherapy is used as adjuvant or neoadjuvant therapy. Another modes of treatment used in cancer therapy is shown in Table I. The various types of therapies caused various types of side effects. The results showed that nausea and vomiting are the most common cancer treatments side effects (59.80 %), followed by combination of nausea vomiting, anemia, and pain suffering (16.44 %), and combination of nausea vomiting and anemia (15.11 %)**.** In breast cancer and non Hodgkins lhympoma (NHL) patients, nausea and vomiting were induced by $\leq$ 1500 mg/m^2 cyclophosphamide and $\geq$ 60 mg/m^2 doxorubicin possessing moderate to high emetogenic potential, and fluorouracil with the dose of 1000 mg/m^2 possessing low to moderate emetogenic potential. Nasopharinx and ovarian cancer patients also experienced nausea induced by 10 mg cisplatin (Jordan *et al.*, 2005). Anemia may directly resulted from agents that induced the suppression of bone marrow to produce blood cells (myelosuppression), such as cyclophosphamide, or agents causing progressive dysfunction of renal tubules which ultimately leads to decreased renal production of endogenous erythropoietin and subsequently reduce production of red blood cells such as cisplatin (Rodgers, 2008; Emadi *et al.*, 2009). Pain suffered may resulted from the use of regimens such as cisplatin that cause peripheral neuropathy, or due to physical sensory from surgical treatment and radiotherapy (British Pain Society, 2010).

The percentage of cancer therapy side effects cost compared to the total direct costs grouped by type of cancer showed that cervical cancer had the highest percentage (8.87 %). Most cervical cancer patients got surgical and radiation therapy, causing anemia and bleeding as the side effects. Blood transfusion was required to manage them. Blood transfusion spent largest cost compared to other therapies like iron supplement or vitamins. It explains why cervical cancer therapy incurring highest cost therapy. The cost percentage in cervical cancer therapy side effects treatments is followed by breast cancer (8.73%). The cost percentage to overcome adverse events in breast cancer therapy was the second largest since many patients used serotonin inhibitor in nausea-vomiting therapy and blood transfusion in anemia therapy. Serotonin inhibitor was the most expensive therapy compared to other antiemetics used in this study, such as metochlopramide and histamine 2 antagonists. Besides, blood transfusion was also the most expensive compared other anemia therapies. Blood transfusion spent $568 to manage anemia because chemotherapy (Weiner *et al.*, 2007).

The cost percentage of side effect treatments compared to the total direct costs grouped based on modes of therapy showed that radiation had the highest percentage (12,09 %). In this study, 2 patients were given this therapy and all of them experienced anemia and bleeding. Thus, they spent a large cost due to blood transfusion, yielding a high average cost percentage compared to the others. Although the average cost of side effects treatments in the combination of chemotherapy-surgery was larger than the side effects treatments cost of combined chemotherapy-radiation, the average total direct costs incurring was higher (Rp 21,563,158). Hence, it resulted in a small cost percentage.

Some drugs are used either alone or in combination in side effects treatments. Research showed that for the treatment of nausea vomiting, mostly used antiemetic was histamin antagonis, but the drugs giving highest total cost was dopamine inhibitor, because many patients were given therapy with brand-name-drugs instead of the generics. Total cost for the treatment of nausea and vomiting was Rp 8,033,779. The anemia therapies used in the study were vitamin B complex, blood transfusion, and iron and folic acid supplementation. Blood transfusion brings the largest costs that incurred to the patients. Bleeding was treated by using tranexamid acid, vitamin K, and carbazochrome with adona. The drug incurring the largest cost was adona used in post surgery or radiation. Total cost for the treatment of anemia and bleeding was Rp 25,895,509.

The next therapy was pain suffering (analgesics) therapy, which use non-steroidal

anti-inflammatory class of analgesics and opioids. The drug incurring the largest cost was ketorolac. Total cost for analgesics therapy was Rp 1,033,530. In one case, the patient developed neutropenia and was treated with Granulocyte Colony Stimulating Factor (G-CSF). Neutropenia therapy using G-CSF brought the most expensive unit price compared to the other therapies, even higher than the blood transfusion unit price. Total cost for the neutropenia therapy is Rp 1,168,750.

Total cost for the treatment of side effects was Rp 36,131,568. Total cases of side effects which the patients suffered, either alone or in combination with the other adverse events, were 121 cases. The average cost for the handling of each case was Rp 298,604. In the cancer inpatient financing, government health insurance paid Rp 2.4 million per cancer patient hospitalization. It already covered all costs, including treatment, examination, fees, etc. But patient must be spent Rp 298,604, on side effects treatments, which made the portion of the cost for cancer therapy and other costs reduced. However, if the need for cancer therapy is abundant, then the hospital has to cover the lack of the cost, and it would be a burden for the hospital. Hospitals should give more attention to the handling of side effects in patients receiving cancer therapy, especially at nadir point. Nadir is a condition when patients suffered the worst condition of side effects. Based on the experiences, usually patients do not feel strong enough to undergo further treatment cycles resulting in the drop out of therapy. Cancer therapy may also highly consider dose selection, by considering the selection of the maximum therapeutic dose that the side effects can still be tolerated by the patients.

This study had several limitations. First, the results of study just described retrospective data, then it couldn't see the side effects therapy profile, meaning that the severity the difference of outcomes representing effectiveness of each drugs to manage cancer treatments side effects did not evaluated. However, this study showed how costly cancer treatments side effect that should be paid by cancer patients. It can be economic burden to them, and side effects decrease patient's clinical condition and quality of life. If patients stopped their chemotherapy cycles because of the side effects, it would bring bad impacts to their health and cause a waste of all costly payment spent in previous treatments. Thus, this study could be a reference to hospital for managing the side effects of cancer treatments. We recommended a prospective design study to evaluate the cost effectiveness and clinical outcome of cancer treatments side effects therapy for further research to gather more information and detailed data.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to The Head of Pharmacy Installation Margono Soekardjo Hospital for supporting data of this study.

REFERENCES

Anonymous, 2009, Cancer caused Biggest Sixth death in Indonesia. Jakarta; [cited 2012 25 April]; Available from: *http://www.depkes.go.id*.

Amy, H.S., 2009, Adverse Effects of Chemotherapy and Targeted Agents. In: Koda-Kimble, M.A., Young, L.Y., Alldredge, B.A., Corelli, R.L., Guglielmo, B.J., Kradjan, W.A., *et al*., editors. *Applied Therapeutics The Clinical Use of Drugs*, 9th Edition, Lippincott Williams & Wilkins, 13-4.

Balmer, C.M., Valley, A.W. and Iannuci, A., 2005, Cancer Treatment and Chemotherapy. In: Dipiro, J.T., Wells, B.G., Talbert, R.L., Atzke, G.R., Posey, L.M., editors. *Pharmacotherapy, A Pathophysiologic Approach*. New York, Mc. Graw-Hill;. pp. 2333.

British Pain Society, 2010, *Cancer Pain Management.* 3 ed. London, British Pain Society.

Dipiro, C.V. and Taylor, A.T., 2005, Nausea and Vomitting. In: Dipiro JT, Wells BG, Talbert RL, Atzke GR, and Posey LM, editors, *Pharmacotherapy, A Pathophysiologic Approach*. New York, Mc. Graw-Hill; pp. 665.

Emadi, A., Jones, R.J. and Brosky, R.A., 2009, Cyclophosphamide and cancer: golden anniversary, *Nat. Rev. Clin. Oncol*., **6**, 638-47.

Garret, K., Tsuruta, K., Walker, S., Jackson, S. and Sweat, M., 2003, Managing Nausea and Vomiting: Curent Strategies, *Crit. Care Nurse*, **23**, 31-50.

Jordan, K., Kasper, C. and Schmoll, H.J., 2005, Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment, *Eur. J.* Cancer, **41**(2), 199-205.

Katzung, B., 2007, *Basic and Clinical Pharmacology.* 10 ed. Jakarta, EGC.

NCI, 2012, Chemotherapy Side Effects Fact Sheets. American Cancer Society; [Cited 5 Mei 2012]; Available from: *http://www.cancer.gov/cancertopics/coping/chemo-side-effects.*

Rodgers, G.M., 2008, Managing Patients with Chemotherapy Induced Anemia, *Adv. Stud. Med*., **8**(10), 346-51.

Weiner, M.G., Ross, S.J., Mathew, J.I., Millman, A.M., Even-Shoshan, O., Fox, K.R., *et al.,* 2007, Estimating The Costs of Chemotherapy-Associated Adverse Event Clusters, *Health Services and Outcomes Research Methodology*, **7**, 1-21.

WHO, 2005, Global Action Against Cancer. Geneva; [cited 25 April 2012]; Available from: *http://www.who.int.*

WHO, 2006, *Worldwide prevalence of anemia 1993-2005*. Atlanta: World Health Organization Global Database on Anemia.