Journal of Cancer Therapy, 2016, 7, 363-369
Published Online June 2016 in SciRes. http://www.scirp.org/journal/jct
http://dx.doi.org/10.4236/jct.2016.76039

Scientific Research Publishing

Risk Factors Associated with In-Hospital Post-Chemotherapy Mortality in Patients with Malignant Musculoskeletal Tumors

Toru Akiyama[1*], Kazuo Saita[1], Hirotaka Chikuda[2], Hiromasa Horiguchi[3], Kiyohide Fushimi[4], Hideo Yasunaga[5]

[1]Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan
[2]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan
[3]Department of Clinical Data Management and Research, Clinical Research Center, National Hospital Organization Headquarters, Tokyo, Japan
[4]Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan
[5]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan
Email: *toruakiyama827@jichi.ac.jp

Received 29 February 2016; accepted 28 May 2016; published 1 June 2016

Abstract

Introduction: Reducing the in-hospital post-chemotherapy mortality rate in patients with malignant musculoskeletal tumors is important for improving treatment outcome. This study aimed to investigate the risk factors associated with in-hospital post-chemotherapy mortality in patients with primary malignant musculoskeletal tumors. Methods: Using a Japanese national inpatient database, we retrospectively identified 5039 patients (2920 men and 2131 women; mean age, 39 years) who underwent curative chemotherapy for malignant musculoskeletal tumors between 2007 and 2010. We extracted data on the patients' characteristics, complications, chemotherapeutic agent use, comorbidities, and in-hospital death. Logistic regression analyses were performed to analyze factors affecting in-hospital post-chemotherapy death in these patients. Results: The overall in-hospital mortality rate was 1.1%. Higher in-hospital mortality rates were significantly associated with a greater volume of blood transfusion (>2500 mL) (odds ratio [OR], 49.71; 95% confidence interval [CI], 22.24 - 111.12; p < 0.001), diabetes mellitus (OR, 3.05; 95% CI: 1.21 - 7.70; p = 0.019), and older age (OR, 3.05; 95% CI, 1.11 - 8.37; p = 0.031). Conclusions: Higher in-hospital post-chemotherapy mortality rates were associated with massive blood transfusion, which was associated with a 16-fold higher risk of in-hospital mortality compared with other risk

*Corresponding author.

How to cite this paper: Akiyama, T., Saita, K., Chikuda, H., Horiguchi, H., Fushimi, K. and Yasunaga, H. (2016) Risk Factors Associated with In-Hospital Post-Chemotherapy Mortality in Patients with Malignant Musculoskeletal Tumors. *Journal of Cancer Therapy*, **7**, 363-369. http://dx.doi.org/10.4236/jct.2016.76039

factors. Blood transfusion volume should be considered an important indicator for deciding whether the next cycle of chemotherapy is administered continuously or not.

Keywords

Chemotherapy, Sarcoma, In-Hospital Mortality, Chemotherapy-Related Death, Japanese Diagnosis Procedure Combination Database

1. Introduction

Chemotherapy plays an essential role in the management of various types of malignant musculoskeletal tumors, and potentially improves long-term patient survival [1]-[3]. To reduce short-term post-chemotherapy mortality, it is important to clarify risk factors associated with in-hospital post-chemotherapy mortality. Previous studies on chemotherapy-related early death in patients with lymphoma, carcinoma, and sarcoma have investigated malignant tumor groups overall but did not focus on specific malignant tumor types.

Neutropenia followed by sepsis is the most frequent cause of death in patients undergoing chemotherapy [4]. Other causes of chemotherapy-related early death have included cardiac, renal, and neurogenic failure; poor performance status scores; advanced age; and pulmonary embolism [4] [5].

However, chemotherapeutic protocols and clinical courses differ between tumor types, and there is little information concerning risk factors associated with post-chemotherapy mortality risk in patients with malignant musculoskeletal tumors.

In the present study, we investigated risk factors associated with in-hospital post-chemotherapy mortality in patients with primary malignant musculoskeletal tumors, using data from a national inpatient database in Japan.

2. Materials and Methods

2.1. Data Source

For this study, we used data from the Japanese Diagnosis Procedure Combination database, details of which have been described previously [6]. Data were collected between July 1 and December 31in each year between 2007-2010. The database contained 2.99 million inpatients from 926 hospitals in 2007, 2.86 million from 855 hospitals in 2008, 2.57 million from 818 hospitals in 2009, and 3.19 million from 952 hospitals in 2010. The database includes the following data: patients' age and sex; diagnoses and comorbidities at the time of admission and complications after admission, which were recorded according to the International Classification of Diseases, Tenth Revision (ICD-10) [in the Japanese language]; procedures; names and doses of drugs administered; blood transfusion volumes; and in-hospital deaths. Because of the anonymous nature of the data, the need for informed consent was waived. This study was approved by the Institutional Review Board at The University of Tokyo.

2.2. Patient Selection

We included all patients with a primary diagnosis of malignant neoplasm of the bone and articular cartilage of limbs (C40), malignant neoplasm of bone and articular cartilage of other and unspecified sites (C41), malignant neoplasm of peripheral nerves and the autonomic nervous system (C47), and malignant neoplasm of other connective and soft tissues (C49). Anticancer agents included cisplatin (CDDP), ADR, methotrexate (MTX), IFM, dacarbazine, and ETO. Combinations of anticancer agents were categorized into the following 8 categories: IFM + ETO, ADR, ADR + CDDP, IFM, IFM + ADR, CDDP, MTX, and others.

2.3. Patients' Background Characteristics

We identified the following comorbidities or procedures that could potentially be associated with in-hospital post-chemotherapy mortality: distant metastasis (including lung, brain, and lymph nodes); administration of G-CSF agents; diabetes mellitus; surgery for malignant musculoskeletal tumors; venous thromboembolism (I80.0-

80.3, A40-41, and D65); chronic HD; and induction of urgent HD. Blood transfusion volume was categorized into the following 3 groups: 0 mL, 1 - 2499 mL, or ≥2500 mL. These factors were surely collected by DPC database system and some of them were not well-studied previously.

2.4. Definitions of Standard and Low-Dose Chemotherapy

In-hospital death following chemotherapy can occur as chemotherapy-related adverse events or as a result of disease progression [4] [7]. Palliative chemotherapy aims to delay disease progression in terminally ill patients, but it is rarely effective and can be harmful [7]. We, therefore, excluded patients with low-dose palliative chemotherapy and only included patients aged >13 years old undergoing standard-dose chemotherapy. Cut-off doses discriminating standard- and low-dose regimens were defined as 6.0 g for MTX, 6.0 g for IFM, 100 mg for CDDP, and 60 mg for ADR, according to the NECO95J regimen or the mesna, doxorubicin, ifosfamide, and dacarbazine regimen. These cut-off values were calculated on the basis of a body surface of 0.8 m^2. This figure was approximately half of the standard body surface area of the Japanese population, being 1.69 m^2 for men and 1.51 m^2 for women [8].

We also excluded patients aged <13 years because of their skeletal immaturity.

2.5. Outcome Measurements

The primary outcome measure was in-hospital mortality.

2.6. Statistical Analyses

For univariate comparisons of patients' characteristics and outcomes between the subgroups, the chi-square test was used for categorical variables and the Wilcoxon rank-sum test was used for continuous variables. Multivariable logistic regression analysis was performed to analyze the concurrent effects of various factors on the occurrence of in-hospital death, while adjusting for the clustering of patients within hospitals using a generalized estimating equation [9]. The threshold for significance was a p-value <0.05. All statistical analyses were performed using SPSS, version 19.0 (IBM Corp., Armonk, NY, USA).

3. Results

We identified 5953 patients (3365 men and 2588 women; mean age, 39 years) who underwent chemotherapy for a malignant musculoskeletal tumor during the study period. We excluded 902 patients with low-dose treatment and included 5051 eligible patients. We excluded patients with hemodialysis (HD) and acute renal failure (ARF) from the final analysis objects because of their high mortality rates and small patient numbers. Seven of 8 patients with chronic HD and one of 4 patients with HD treatment for ARF died. Thus, the final analysis population included 5039 eligible patients.

Patients' background characteristics and in-hospital mortality rates are shown in **Table 1**. Overall, the in-hospital mortality rate was 1.1%, and 80% of the patients were aged <59 years. Blood transfusions were not required in 79%. Granulocyte-colony stimulating factor (G-CSF) was administered to 55% of the patients. The main drug combinations administered were ifosfamide (IFM) plus doxorubicin hydrochloride (ADR), IFM alone, and IFM plus etoposide (ETO). Distant metastasis, G-CSF administration, diabetes mellitus and greater volumes of blood transfusion had significant effect on in-hospital mortality. Different drug combinations did not have any significant effect on in-hospital mortality rates.

Table 2 shows the results of the logistic regression analysis. Higher mortality was significantly associated with older age, distant metastasis, diabetes mellitus, and greater volumes of blood transfusion, but not with G-CSF administration. The odds ratio for blood transfusion (>2500 mL) was 49.71 (95% confidence interval, 22.24 - 111.12) when compared with no blood transfusion.

4. Discussion

In the present study, we utilized the data from a Japanese national inpatient database to elucidate risk factors associated with in-hospital post-chemotherapy mortality in patients with malignant musculoskeletal tumors. The overall in-hospital mortality rate was 1.1%, and massive blood transfusion was significantly associated with

Table 1. In-hospital mortality.

		In-hospital mortality			
		N	*n*	(%)	*p*-value
All		5039	53	(1.1)	
Sex	Male	2913	34	(1.2)	
	Female	2126	19	(0.9)	0.347
Age (years)	≤59	4032	41	(1.0)	
	60 - 69	763	6	(0.8)	
	≥70	244	6	(2.5)	0.074
Distant metastasis	No	4102	33	(0.8)	
	Yes	937	20	(2.1)	<0.001
G-CSF	No	2279	10	(0.4)	
	Yes	2760	43	(1.6)	<0.001
Diabetes mellitus	No	4853	44	(0.9)	
	Yes	186	9	(4.8)	<0.001
Surgery	No	4670	50	(1.1)	
	Yes	369	3	(0.8)	0.640
Deep vein thrombosis	No	4994	52	(1.0)	
	Yes	45	1	(2.2)	0.439
Blood transfusion (mL)	0	3998	10	(0.3)	
	1 - 2499	728	11	(1.5)	
	≥2500	313	32	(10.2)	<0.001
Chemotherapy	IFM + ADR	1411	18	(1.3)	
	IFM	884	8	(0.9)	
	IFM + ETO	753	4	(0.5)	
	ADR	545	4	(0.7)	
	ADR + CDDP	448	4	(0.9)	
	CDDP	200	2	(1.0)	
	MTX	198	1	(0.5)	
	Others	600	12	(2.3)	0.237

G-CSF, granulocyte-colony stimulating factor; IFM, ifosfamide; ETO, etoposide; ADR, doxorubicin hydrochloride; CDDP, cisplatin; MTX, methotrexate.

Table 2. Logistic regression analysis for in-hospital mortality.

		In-hospital mortality		
		OR	95% CI	*p*-value
Age (years)	≤59	Reference		
	60 - 69	1.39	0.54 - 3.53	0.495
	≥70	3.05	1.11 - 8.37	0.031
Distant metastasis	No	Reference		
	Yes	3.05	1.69 - 5.49	<0.001
G-CSF	No	Reference		
	Yes	1.01	0.44 - 2.31	0.981
Diabetes mellitus	No	Reference		
	Yes	3.05	1.21 - 7.70	0.019
Blood transfusion (mL)	0	Reference		
	1 - 2499	6.02	2.90 - 12.51	<0.001
	≥2500	49.71	22.24 - 111.12	<0.001

OR, odds ratio; CI, confidence interval; G-CSF, granulocyte-colony stimulating factor.

in-hospital mortality. Other risk factors associated with increased in-hospital mortality included distant metastasis, diabetes mellitus, and greater age (≥70 years).

Published data relating to the outcomes of systemic anticancer therapies have been limited. Previous studies investigated post-chemotherapy early death for all malignant tumors, and several studies have assessed early mortality specific to lung cancer [4] [5]. However, to our knowledge, studies investigating post-chemotherapy early mortality in patients with malignant musculoskeletal tumors have not been published, most probably because of the rarity of the disease. Post-chemotherapy early mortality for all malignant tumors has been reported as ≤10% [4] [5] [8]. Our data demonstrated that in-hospital post-chemotherapy mortality in patients with malignant musculoskeletal tumors was significantly lower than that for other malignant tumors.

Blood transfusion volume has not been reported previously as a risk factor for in-hospital post-chemotherapy mortality for malignant tumors. However, in the present study, a greater blood transfusion volume (≥2500 mL) elicited a 16 fold higher risk of in-hospital mortality compared with other identified risk factors. Myelosuppression is a common adverse effect of chemotherapy that can induce severe anemia and thrombocytopenia, which require blood transfusion [10] [11]. Although anemia can have a profound effect on many aspects of the patients' quality of life, severe thrombocytopenia has been reported as a life-threatening complication of cancer chemotherapy [11]-[13]. Situations requiring high blood transfusion volumes can include severe myelosuppression as well as serious general conditions and terminal stage diseases. Our findings suggest that these types of situation could be associated with a high rate of in-hospital post-chemotherapy death. Although previous reports have noted severe thrombocytopenia as a risk factor that increases in-hospital death, our data suggest that severe anemia might also be a risk factor for increasing in-hospital death.

Our study has several limitations that are inherent to all administrative database studies. First, the database does not provide important clinical data such as the pathological case data and the individuals' performance status. Second, the database is restricted to information on in-hospital and major complications only and does not provide any information pertaining to the patients' conditions before admission and after discharge. Third, the database does not provide data on the physicians' intent to administer curative or palliative chemotherapy (*i.e.*, individualized chemotherapy). Despite these limitations, our study has provided important information to pre-

vent harmful chemotherapy treatment in patients with malignant musculoskeletal tumors.

5. Conclusion

Massive blood transfusion was significantly associated with in-hospital post-chemotherapy mortality. To date, massive blood transfusion has not been reported as a risk factor for in-hospital post-chemotherapy mortality in patients with malignant musculoskeletal tumors. Thus, blood transfusion volume is an important factor to enable better treatment decisions on whether to administer the next cycle of continuous chemotherapy in these patients.

Acknowledgements

This study was supported by a Grant-in-Aid for Research on Policy Planning and Evaluation from the Ministry of Health, Labour and Welfare in Japan (grant no.: H22-Policy-031), a Grant-in-Aid for Scientific Research B (No. 22390131) from the Ministry of Education, Culture, Sports, Science, and Technology, and a Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST program) from the Council for Science and Technology Policy in Japan (grant no.: 0301002001001).

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

HY, HH, and KF collected the data. TA, HC, HY, and KS designed the study, analyzed and interpreted the data, and drafted the manuscript. All authors had full access to all data (including the statistical reports and tables) and take full responsibility for the integrity of the data and the accuracy of the data analysis.

References

[1] Arndt, C.A. and Crist, W.M. (1999) Common Musculoskeletal Tumors of Childhood and Adolescence. *New England Journal of Medicine*, **341**, 342-352. http://dx.doi.org/10.1056/NEJM199907293410507

[2] Bacci, G., Ferrari, S., Bertoni, F., Rimondini, S., Longhi, A., Bacchini, P., Forni, C., Manfrini, M., Donati, D. and Picci, P. (2000) Prognostic Factors in Nonmetastatic Ewing's Sarcoma of Bone Treated with Adjuvant Chemotherapy: Analysis of 359 Patients at the Istituto Ortopedico Rizzoli. *Journal of Clinical Oncology*, **18**, 4-11.

[3] Ogura, K., Goto, T., Imanishi, J., Shinoda, Y., Okuma, T., Tsuda, Y., Kobayashi, H., Akiyama, T., Hirata, M., Yamamoto, A. and Kawano, H. (2013) Neoadjuvant and Adjuvant Chemotherapy with Modified Mesna, Adriamycin, Ifosfamide, and Dacarbazine (MAID) Regimen for Adult High-Grade Non-Small Round Cell Soft Tissue Sarcomas. *International Journal of Clinical Oncology*, **18**, 170-176. http://dx.doi.org/10.1007/s10147-011-0360-x

[4] Ray-Coquard, I., Ghesquiere, H., Bachelot, T., Borg, C., Biron, P., Sebban, C., LeCesne, A., Chauvin, F., Blay, J.Y. and ELYPSE Study Group (2001) Identification of Patients at Risk for Early Death after Conventional Chemotherapy in Solid Tumours and Lymphomas. *British Journal of Cancer*, **85**, 816-822. http://dx.doi.org/10.1054/bjoc.2001.2011

[5] Yoong, J., Seah, J.A., Hamilton, K., Teo, L.N. and Chong, G. (2012) Mortality within 30 Days of Receiving Systemic Anti-Cancer Therapy at a Regional Oncology Unit: What Have We Learned? *Asia-Pacific Journal of Clinical Oncology*, **8**, 325-329. http://dx.doi.org/10.1111/j.1743-7563.2011.01498.x

[6] Chikuda, H., Yasunaga, H., Horiguchi, H., Takeshita, K., Kawaguchi, H., Matsuda, S. and Nakamura, K. (2012) Mortality and Morbidity in Dialysis-Dependent Patients Undergoing Spinal Surgery: Analysis of a National Administrative Database in Japan. *The Journal of Bone and Joint Surgery, American Volume*, **94**, 433-438. http://dx.doi.org/10.2106/JBJS.K.00183

[7] Wright, A.A., Zhang, B., Keating, N.L., Weeks, J.C. and Prigerson, H.G. (2014) Associations between Palliative Chemotherapy and Adult Cancer Patients' End of Life Care and Place of Death: Prospective Cohort Study. *BMJ*, **348**, g1219. http://dx.doi.org/10.1136/bmj.g1219

[8] Research Center for Chemical Risk Management (2007) Body Surface Areas. In: National Institute of Advanced Industrial Science and Technology, Ed., *Japanese Exposure Factors Handbook*. https://unit.aist.go.jp/riss/crm/exposurefactors/english_summary.html

[9] Hubbard, A.E., Ahern, J., Fleischer, N.L., Van der Laan, M., Lippman, S.A., Jewell, N., Bruckner, T. and Satariano, W.A. (2010) To GEE or Not to GEE: Comparing Population Average and Mixed Models for Estimating the Associations between Neighborhood Risk Factors and Health. *Epidemiology*, **21**, 467-474.

http://dx.doi.org/10.1097/EDE.0b013e3181caeb90

[10] Vadhan-Raj, S., Papadopoulos, N.E., Burgess, M.A., Linke, K.A., Patel, S.R., Hays, C., Arcenas, A., Plager, C., Kudelka, A.P., Hittelman, W.N., Broxmeyer, H.E., Williams, D.E., Garrison, L. and Benjamin, R.S. (1994) Effects of PIXY321, a Granulocyte-Macrophage Colony-Stimulating Factor/Interleukin-3 Fusion Protein, on Chemotherapy-Induced Multilineage Myelosuppression in Patients with Sarcoma. *Journal of Clinical Oncology*, **12**, 715-724.

[11] Demetri, G.D. (2001) Anaemia and Its Functional Consequences in Cancer Patients: Current Challenges in Management and Prospects for Improving Therapy. *British Journal of Cancer*, **84**, 31-37. http://dx.doi.org/10.1054/bjoc.2001.1750

[12] Blay, J.Y., Le Cesne, A., Mermet, C., Maugard, C., Ravaud, A., Chevreau, C., Sebban, C., Guastalla, J., Biron, P. and Ray-Coquard, I. (1998) A Risk Model for Thrombocytopenia Requiring Platelet Transfusion after Cytotoxic Chemotherapy. *Blood*, **92**, 405-410.

[13] Alexandre, J., Gross-Goupil, M., Falissard, B., Nguyen, M.L., Gornet, J.M., Misset, J.L. and Goldwasser, F. (2003) Evaluation of the Nutritional and Inflammatory Status in Cancer Patients for the Risk Assessment of Severe Haematological Toxicity Following Chemotherapy. *Annals of Oncology*, **14**, 36-41. http://dx.doi.org/10.1093/annonc/mdg013