Int J Clin Exp Med 2017;10(5):8648-8655
www.ijcem.com /ISSN:1940-5901/IJCEM0037277

Original Article

Intra-hospital survival of non-Hodgkin's lymphoma patients with febrile neutropenia

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Received August 4, 2016; Accepted October 30, 2016; Epub May 15, 2017; Published May 30, 2017

Abstract: Background: Recent data regarding the survival of non-Hodgkin's lymphoma (NHL) patients with febrile neutropenia (FN) are lacking. The purpose of this study was to investigate the prognostic factors affecting survival in FN patients with NHL. Material and methods: We retrospectively analyzed 265 NHL patients with FN who were hospitalized and received chemotherapy at the Sun Yat-sen University Cancer Center from March 2012 to November 2015. Results: The overall intra-hospital mortality was 12.1%. For univariate analysis, there were significant differences between survivors and non-survivors regarding the chemotherapy intent, level of procalcitonin (PCT), infection evidence, pneumonia, multi-site hospital infection, duration of grade IV myelosuppression, duration of neutropenia, duration of hospital stay, duration of fever, fungal infection, and ICU support. In multiple logistic regression analysis, non-curative chemotherapy (OR: 5.504, [95% CI: 1.780-17.019], P=0.003), a high level of PCT (OR: 56.598, [95% CI 14.455-221.615], P=0.000), and long-term myelosuppression (OR: 21.615, [95% CI: 5.383-86.804], P=0.000) were the important prognostic factors in NHL patients with FN. Conclusion: Our results showed that the outcome of NHL patients with FN and hospitalization depends on the chemotherapy intent, level of PCT and duration of myelosuppression.

Keywords: Non-Hodgkin's lymphoma, febrile neutropenia, intra-hospital survival, prognostic factors

Introduction

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of lympho-proliferative disorders originating from B lymphocytes, T lymphocytes, or natural killer cells [1, 2]. The key and most important treatment for patients with NHL is multidrug systemic chemotherapy, among which a regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) is considered to be a standard treatment [1, 3]. A common and serious clinical consequence of myelosuppression chemotherapy is neutropenia, which is defined as an absolute neutrophil count (ANC) $<0.5\times10^9$/L, often resulting in hospitalization and the administration of empiric broad-spectrum antibiotics [4-8]. Previous studies have reported that patients with a solid tumor or a hematologic malignancy with febrile neutropenia (FN) have high mortality rates [9-15]. In response to this clinical problem, research has helped to identify prognostic factors related to intra-hospital mortality. The results showed that elderly patients, hypertension, hypovolemia, fungal infections, septic shock, and bacteremia in the setting of neutropenia were significant risk factors for intra-hospital mortality [12, 16-20].

A better understanding of mortality trends and factors associated with mortality will aid clinicians in formulating an effective therapeutic plan to further reduce the risk of both mortality and major complications associated with FN. Previous studies have assessed a series of consecutive FN cancer patients, including those with a combination of solid tumor and hematologic malignancy patients. To our knowledge, compared with solid tumors, the diagnosis of hematological malignancies, particularly AML and NHL, was associated with a three-fold increased risk of mortality [21]. Recent data

regarding the survival of the subpopulation of NHL patients with FN are scarce.

The objective of this study was to identify the factors that are associated with the inpatient mortality of FN in NHL patients receiving chemotherapy based on patient-related, chemotherapy-related, and infectious characteristics.

Materials and methods

Patient eligibility

We retrospectively analyzed 265 patients with NHL who were hospitalized and received chemotherapy at the Sun Yat-sen University Cancer Center from March 2012 to November 2015. The patients who were enrolled in this study met the following inclusion criteria: they were adult patients with NHL (16 years or older); they all had neutropenia and fever during the first chemotherapy course according to the Infectious Diseases Society of America (IDSA) Fever and Neutropenia Guideline that was updated in 2010 [22], and in which neutropenia was defined as an ANC less than 0.5×10^9/L; fever was defined as an axillary temperature >38.0°C lasting more than 1 h per day or ≥38.3°C in a single record. In this study, patients were divided into two groups: survival (n=233) and non-survival (n=32).

Data collection

During the FN period, patient characteristics-including demographics, clinical data and outcomes-were collected from the patients' electronic medical records. Regarding the level of PCT, the patients were split into two groups (≤2 ng/ml or >2 ng/ml) [23]. According to the level of CRP, the patients were also divided into two groups (≤100 mg/L or >100 mg/L). The patients were further divided into two groups based on the duration of grade IV myelosuppression (≤10 days or >10 days), duration of grade IV neutropenia (≤10 days or >10 days), length of hospital stay (≤1 month or >1 month), and duration of fever (≤5 days or >5 days). These cut-off points were determined by the ROC curve and Youden's index. For clinically documented sites of infection, multi-site hospital infection indicated two or more clinically documented sites; other factors included pneumonia, the gastrointestinal tract, oral mucositis, and miscellaneous. In this study, ICU support indicated that patients were admitted to the ICU or needed hemodynamic support, ventilator support or bedside continuous blood purification. Other covariates included age, gender, classification of non-Hodgkin's lymphoma, tumor stage (I-II, III-IV), basic disease (chronic hepatitis B, type 2 diabetes mellitus, and hypertension), B symptoms, relapse during hospitalization, chemotherapy regimen, chemotherapy intent (curative chemotherapy or non-curative chemotherapy, including adjuvant, neoadjuvant or palliative chemotherapy), infection evidence (classified as fever of unknown origin (FUO), microbiologically documented infection (MDI) and clinically documented infection (CDI)), definite invasive fungal disease, antimicrobial prophylaxis, antibiotics therapy at FN presentation, and therapeutic granulocyte colony stimulating factor (G-CSF) prescription. The audit outcome of interest was inpatient mortality.

Statistics analysis

All statistical analyses were performed using SPSS ver. 13.0.1 (SPSS Inc., Chicago, IL). The normality of all variables was studied using the Kolmogorov-Smirnov test. Data were expressed as the mean ± SD or median (range) for quantitative and qualitative variables, respectively. Univariate comparisons between survivors and non-survivors were performed using the two-tailed independent samples t-test, Mann-Whitney U-test or chi-squared test, as appropriate. Variables with a *P*-value less than 0.05 for the difference were included in the multivariate analysis, which was performed based on a logistic regression model to identify factors related to mortality, and odds ratios (ORs) with 95% confidence intervals were computed. A *P*-value less than 0.05 was considered to be statistically significant in this multivariate analysis.

Results

General characteristics of the sample

A total of 265 patients were analyzed in this study. There were 163 (61.5%) males and 102 (38.5%) female patients. The mean age was 39 years (range, 16-84 years). Most of the patients were classified as having tumor stages III and IV (84.2%). There were 164 (61.9%) patients with B-cell lymphoma and 101 (38.1%) patients with T-cell and NK-cell lymphoma; of these, the

Table 1. Patients' characteristics; survivors and non-survivors

	Total N=265	Survivors N=233	Non-survivors N=32	*P*-value
Age (years, mean ± SD)	39±19	38±19	42±19	0.281
Gender, male/female	163/102	143/90	20/12	0.902
Classification of non-hodgkin lymphoma*				
Diffuse large B-cell lymphoma	72	65	7	
Burkitt lymphoma	36	32	4	
Mature B-cell lymphoma	27	18	9	
Precursor B-cell lymphoma	15	13	2	
Gray zone lymphoma	14	13	1	
Precursor T-cell lymphoma	36	31	5	
Mature NK/T-cell lymphoma	65	61	4	
Tumor stage				0.131
I-II	42	34	8	
III-IV	223	199	24	
Basic disease				
Chronic hepatitis B	35	29	6	
Type 2 diabetes mellitus	19	19	0	
Hypertension	19	16	3	
B symptoms	52	44	8	0.414
Chemotherapy regimen				
CHOP ± rituximab	98	84	14	
EPOCH ± rituximab	35	28	7	
BEAM	45	41	4	
ICE	41	36	5	
GDP	15	14	1	
Others	31	30	1	
Chemotherapy intent				0.001
Curative	202	185	17	
Non-curative	63	48	15	

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; BEAM, carmustine, etoposide, cytarabine, melphalan; ICE, ifosfamide, carboplatin, etoposide; GDP, gemcitabine, dexamethasone, cisplatin. *Classification of non-Hodgkin lymphoma was according to the Revised European-American-World Health Organization classifi cation of lymphoid neoplasms (2008).

most common type of B-cell lymphoma was diffuse large B-cell lymphoma (43.9%). Fifty-two (19.6%) patients had constitutional symptoms (B symptoms). Concerning the underlying disease among the patients in this study, 35 cases had chronic hepatitis B, 19 cases had type 2 diabetes mellitus, and 19 cases had hypertension. The most frequent chemotherapy regimen was the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone; 37.0% of the patients) followed by the BEAM regimen (carmustine, etoposide, cytarabine, and melphalan) (17.0%). There were 202 (76.2%) patients who received curative chemotherapy, while the remainder (23.8%) received adjuvant, neoadjuvant or palliative chemotherapy.

Survivors generally had a low level of PCT and CRP. Most cases of infections in the study were confirmed by a positive microbiological assessment such as blood culture (MDI, 40.0%) or focal infection (CDI, 22.6%), while 99 (37.4%) patients exhibited fever with no detectable cause (FUO). The main infectious site was the lung (27.2%), and 19 patients had two or more infectious sites. Sixteen patients were documented with definite invasive fungal disease. One hundred and fourteen patients received prophylactic antibiotic therapy, and 256 patients received antibiotic therapy at FN presentation, including 58 cases with monotherapy and 198 cases with combination therapy. Most patients (95.5%) used G-CSF while at the hospi-

Table 2. Infectious characteristics; survivors and non-survivors

	Total N=265	Survivors N=233	Non-survivors N=32	*P*-value
PCT				<0.001
≤2	205	199	6	
>2	60	34	26	
CRP*				0.564
≤100	103	88	15	
>100	79	65	14	
Infection evidence				<0.001
FUO	99	98	1	
CDI	60	55	5	
MDI	106	80	26	
Clinically documented sites of infection				
Pneumonia	72	55	17	<0.001
Gastrointestinal tract (diarrhea)	32	31	1	0.224
Oral mucositis	12	12	0	0.375
Miscellaneous	17	15	2	0.703
Multi-site hospital infection	19	10	9	<0.001
Fungal infection	16	11	5	0.015
Duration of grade IV myelosuppression (days)				<0.001
≤10	233	216	17	
>10	32	17	15	
Duration of neutropenia (days)				0.001
≤10	254	227	27	
>10	11	6	5	
Duration of hospital stay (months)				0.016
≤1	209	189	20	
>1	56	44	12	
Duration of fever (days)				<0.001
≤5	186	173	13	
>5	79	60	19	
Prior antibiotics	114	105	9	0.070
Antibiotics therapy				0.174
No	9	9	0	
Monotherapy	58	54	4	
Combination therapy	198	170	28	
GSF	253	221	32	0.189
ICU support	31	13	18	<0.001

*The data are available in 182 patients. PCT, procalcitonin; CRP, C-reactive protein; UFO, fever of unknown origin; MDI, microbiologically documented infection; CDI, clinically documented infection; GSF, granulocyte stimula-ting factor; ICU, intensive care unit. *Grade IV myelosuppression: hemoglobin <65 g/L and/or white blood cell count (WBC) $<10^9$/L and/or absolute neutrophil count (ANC) $<0.5\times10^9$/L and/or platelet count (PLT) $<25\times10^9$/L.

tal. The length of hospital stay (LOS) was less than one month for 209 patients (78.9%), and the duration of fever was more than 5 days for 79 patients. There were 43 FN episodes (16.2%) in which the patient developed septic shock; of these, 24 patients (9.1%) died from the rapid progression of infection. There were 31 patients with FN admitted to the ICU; of these, 30 patients developed septic shock and required hemodynamic support, 19 patients needed ventilator support, and six patients underwent bedside continuous blood purification. Eighteen patients died during the ICU support period, with an ICU mortality of 58.1%. The

Table 3. Multiple logistics regerssion analysis

	P	OR	95% CI	
			Lower	Upper
Non-curative chemotherapy	0.003	5.504	1.780	17.019
PCT >2	0.000	56.598	14.455	221.65
Grade IV myelosuppression* >10 days	0.000	21.615	5.383	86.804

PCT, procalcitonin. *Grade IV myelosuppression: hemoglobin <65 g/L and/or white blood cell count (WBC) $<10^9$/L and/or absolute neutrophil count (ANC) $<0.5\times10^9$/L and/or platelet count (PLT) $<25\times10^9$/L.

overall treatment success rate was 87.9%. All individuals who experienced TF died, of whom 22 patients died directly from the progression of infection and 10 patients died from tumor complications combined with infections during the recovery from neutropenia. During the hospital stay, all of the patients were followed for a median time of 22 days (range, 3 to 112 days); thirty-two patients (12.1%) died, with a median overall survival of 21 days (range, 3 to 71 days).

Univariate analysis

First, the candidate patient-related and chemotherapy-related predictors of the survival of the NHL patients with FN are shown in **Table 1**. There was no difference in age, sex, tumor stage, B symptoms between survivors and non-survivors. Regarding the chemotherapy-related variables, the chemotherapy intent was associated with the outcome (P=0.001). Next, univariate analysis including infectious characteristics and comparing survivors and non-survivors was performed and is illustrated in **Table 2**. There were significant differences in the level of PCT (P<0.001), infection evidence (P< 0.001), pneumonia (P<0.001), multi-site hospital infection (P<0.001), fungal infection (P= 0.015), duration of grade IV myelosuppression (P<0.001), duration of neutropenia (P=0.001), duration of hospital stay (P=0.016), duration of fever (P<0.001), and ICU support (P<0.001). There were no differences between survivors and non-survivors in the level of CRP, other infection (e.g., gastrointestinal tract infection, oral mucositis, skin infection, ear-nose-throat (ENT) infection, catheter-related blood stream infection, and urinary tract infection), antimicrobial prophylaxis, antibiotics therapy at FN presentation, and therapeutic granulocyte colony stimulating factor (G-CSF) prescription (P>0.05).

Multivariate analysis

As shown in **Table 3**, multiple logistic regression analysis identified the following factors to be significantly associated with a higher mortality: non-curative chemotherapy (OR: 5.504, [95% CI: 1.780-17.019], P=0.003), a high level of PCT (OR: 56.598, [95% CI 14.455-221.615], P=0.000), and long-term myelosuppression (OR: 21.615, [95% CI: 5.383-86.804], P=0.000).

Discussion

To our knowledge, this is the first study to evaluate the outcome among febrile neutropenia admissions with NHL. In this three-year retrospective study, a high inpatient mortality of 12.1% was observed in NHL patients with FN. Simultaneously, the clinical practice data indicated that many infectious characteristics were related to in-hospital mortality, while most of the patient- and chemotherapy-related factors were not associated with the outcome of FN patients. Finally, non-curative chemotherapy, a high level of PCT, and long-term myelosuppression were found to be associated with a poor outcome in a multivariate analysis.

A recent study reported that the crude incidence rates of early mortality were significantly higher (15%) for patients with FN than for controls for all tumor types [24]. FN is a common adverse effect of myelosuppressive chemotherapy and undoubtedly significantly increases the inpatient mortality as a major complication. Although with the improvement of prophylactic/therapeutic colony-stimulating factors and use of newer, less toxic chemotherapy regimens in recent years, the inpatient mortality rate for FN patients has not been severely affected [25-28]. The inpatient mortality rate of 12.1% of the NHL patients with FN in the current study appears to be consistent with the mortality rates of 6.6% to 14% reported in several studies with a larger series of consecutive FN cancer patients, including both solid tumor and hematologic malignancy patients [15, 21, 29, 30]. In addition, the in-hospital mortality rate in the current study was significantly high-

er than the data reported in breast cancer (2.6%) [31].

In recent years, the clinical variables age group, cancer type, bacteremia/sepsis, pneumonia, hypotension, hepatic disease, renal disease, and heart disease were found to indicate a poor outcome in overall cancer patient cohort admitted with FN [15, 30]. In our study, bacteremia and pneumonia were among the variables confirmed to be related to mortality in NHL patients with FN. The Infectious Diseases Society of America (IDSA) Fever and Neutropenia Guideline updated in 2010 indicated that all patients who present with fever and neutropenia should be treated with broad-spectrum empirical antibiotics promptly (within 2 h of presentation) [22]. However, in the present study, neither antibiotics therapy nor the therapeutic granulocyte colony stimulating factor (G-CSF) prescription were related to inpatient mortality, a finding that corresponds with the analysis of Mhaskar R, who reported that the use of CSF plus antibiotics in individuals with chemotherapy-induced febrile neutropenia had no effect on the overall mortality but reduced the amount of time participants stayed in the hospital and improved their ability to achieve neutrophil recovery [32]. Differences in the available antibiotics, predominant pathogens, and/or health care-associated economic conditions could have contributed to this situation.

The three predictive factors for survival in our study were non-curative chemotherapy, a high level of PCT, and long-term myelosuppression. Obviously, some of those variables were closely associated with each other; the chances of infection increase in NHL patients with FN due to long-term myelosuppression. Furthermore, infection could certainly have an effect on the level of PCT. Accordingly, long-term grade IV myelosuppression may be an important risk factor for the inpatient mortality of NHL patients with FN. In our study, there were 32 patients whose duration of grade IV myelosuppression was more than 10 days; for these patients, the inpatient mortality was high (46.9%). Anticancer drugs causebone marrow myelosuppression, leading to a reduction in hematopoietic tissue activity and a corresponding decline in cell production. The direct or indirect suppression of granulocytes has potential for multiple negative clinical consequences, ranging from infection to life-threatening septic shock [33]. Moreover, a high level of PCT is the second prognostic factor for survival in our study, and our previous study has reported that a significantly elevated PCT level is helpful for detecting infection in patients with NHL with newly developed FN and indicate a poor prognosis [23], findings that are consistent with those of the present study. PCT as an early marker for the prediction of infection and prognosis could have contributed to clinical vigilance and immediate treatment, which are universal keys to managing neutropenic patients with fever and infection [22].

Non-curative chemotherapy, including adjuvant, neoadjuvant and palliative chemotherapy regimens, indicated a poor outcome in the current study. This result is not surprising because curative chemotherapy is relatively intensive in regard to therapy dose and efficacy. Additionally, most NHL patients receiving palliative chemotherapy regimens seem to be elderly patients with advanced malignant tumors, a circumstance that may contributed to a poor prognosis.

Once FN patients developed a severe infection, septic shock or organ failure, they usually need ICU support, and whether those patients will benefit from ICU monitoring, including hemodynamic support, ventilator support and bedside continuous blood purification, remains in dispute [34-36]. In this study, we reported a high ICU mortality; more than half of the patients who were admitted into ICU died, indicating that FN patients could rarely benefit from ICU support once they developed serious complications. Alternatively, attention should be paid to the prevention of severe infection early in FN patients.

Our study has several limitations. First, this work was a retrospective study conducted at a single center; some detailed clinical information is unavailable, including the cause of death, timing of event, and utilization of specific medications. Second, we did not analyze the impact of FN beyond inpatient mortality. In fact, the length of stay, financial costs, long-term survival, and quality of life after discharge must be included for an ideal assessment of the patient outcome. Third, our small sample size (n=265) produced limited statistical power.

Conclusion

In this study, the intra-hospital mortality rate was 12.1%. Chemotherapy-induced FN remains a severe cause of substantial mortality among NHL patients. Our results show that the outcome of NHL patients with FN and hospitalization depends on the chemotherapy intent, level of PCT, duration of myelosuppression.

Acknowledgements

This study was financially supported by the Science & Technology Project of Guangdong Province (2010B030700051) (2013B022000042).

Disclosure of conflict of interest

None.

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