RESEARCH ARTICLE

Association of Chemotherapy-induced Leucopenia with Treatment Outcomes in Advanced Non-small-cell lung Cancer Cases Receiving the NP Regimen

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Abstract

Background: Chemotherapy induced leutropenia has been shown to be associated with improved treatment outcomes in selected solid tumors. We studied the association of chemotherapy induced leutropenia with treatment related outcomes in advanced non-small-cell lung cancer. Methods: This is a prospective analysis of patients receiving chemotherapy for advanced NSCLC at the Shandong Cancer Hospital from 2005-07.The chemotherapy included cisplatin 35 mg/m^2, IV on $d_{1,2}$ and vinorelbine 25 mg/m^2 IV on $d_{1,8}$ every 21 days. Patients were stratified into three groups (A) those experiencing grades 0 leucopenia, group (B) grades 1-2 and group (C) grades 3-4. The outcomes studied were response rate (RR), disease control rate (DCR), and time to progression (TTP). Results: 128 patients were studied. The RRs in groups A, B and C were 30.8%, 56.8% and 71.4%, respectively, p=0.010. The DCRs were 61.5%, 83.8% and 92.9%, respectively, p=0.009 and the median TTPs were 150 days (95%CI: 91-209), 189 days (95%CI: 181-197) and 207 days (95%CI: 172-242), p=0.009. The differences in RR and TTP were significant. In patients whose CIL kept on 10 days at least, the TTP was significantly prolonged, p=0.0213, and the same was the case for those experiencing grades 1-2 leucopenia and ECOG 0, p=0.0412. Conclusions: Occurrence of CIL correlated with RR and TTP in patients with advanced NSCLC receiving cisplatin and vinorelbine chemotherapy, especially in patients experiencing grades 1-2 leucopenia and ECOG 0, and the same for those with CIL persisting for 10 days at least. CIL could be a biological measure of drug activity and a marker of efficacy.

Keywords: Chemotherapy - leucopenia - efficacy - non-small-cell lung cancer

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Introduction

Lung cancer is the most common malignancy in the world, and non-small-cell lung cancer (NSCLC) accounts for approximately 85 percent. Most patients are already advanced when diagnosed. Chemotherapy is a mainstay of treatment in the majority of patients. At present, a two-drug regimen consisting of a platinum agent is regarded standard treatment for adults with good performance status (Delbaldo et al., 2004; Pfister et al., 2004), resulting in an extremely toxic physiologic environment and placing patients at high risk for adverse events. Chemotherapy induced leucopenia (CIL) is a common and significant adverse effect of chemotherapy, defined as a leucopenia count of $<4.00\times10^9$/L, and it can put patients at risk for severe infection (Lyman et al., 2010; Lyman and Kleiner, 2011). It is also the major dose-limiting toxicity, and it is frequently managed by reducing or delaying the chemotherapy (Delbaldo et al., 2004; Hangaishi, 2011; Saloustros et al., 2011), which can result in lower disease-free and overall survival (Kvinnsland et al., 1999;Gurney 2002; Schiller et al., 2002; Gridelli et al., 2003; Pfister et al., 2004),

However, research (Shitara et al., 2011) on breast cancer (Saarto et al., 1997; Poikonen et al., 1999; Cameron et al., 2003; Shitara et al., 2010; Han et al., 2012), small-cell lung cancer (Banerji et al., 2006), osteosarcoma (Ratain, 1998), ovarian cancer (Sawyer and Ratain., 2001) have shown the association between chemotherapy-induced neutropenia and better clinical outcome for patients. It is not associated with increased risk for death (Souza-Dantas et al., 2011). CIL can be used as a biological measure of drug activity and a marker of efficacy. Individualizing cytotoxic chemotherapy can be achieved according to CIL. Retrospective studies on NSCLC got the similar results (Gridelli et al., 2003a; Gridelli et al., 2003b; Di Maio et al., 2005; Camps et al., 2006; Kishida et al., 2009). But it has no prospective random trials on this so far. Then, we designed this prospective study to evaluate the association of CIL on treatment outcomes in advanced NSCLC treated with NP regimen. The preliminary results are reported as below.

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Materials and Methods

Population

128 patients with advanced NSCLC were treated with NP regimen as first line chemotherapy from 2005-7 in Shandong Tumor Hospital. All patients were diagnosed by cytology and/or pathology. The median age was 54 years (range 37-77 years). The male: female ration was 90:38; IIIB:IV was 68:60. 72 cases were adenocarcinoma,48 cases were squamous carcinoma, the others were 8 cases. All patients were expected to survive for more than 3 months and no history of chemotherapy, with measurable objective lesions and a good baseline performance status of 0-1 according to the Eastern Cooperative Group scale. Liver and kidney function and blood count was normal, no brain metastases. All patients gave written informed consent. Excluding criteria: abandoning chemotherapy; progressing with in 3 cycles; preventive use of G-CSF; bone marrow dysfunction or splenomegaly. The dosage, time, image data and the extent of leucopenia were registered. This study was approved by ethics committees of Shandong Cancer Hospital.

Chemotherapy

25mg/m^2 vinorelbine was given intravenously on days 1 and 8, 35mg/m^2 cisplatin on days 1 and 2 of a 21-days cycle for a maximum of six cycles. Blood count, urine, liver and kidney function, ECG was routinely checked before and after chemotherapy. Blood count was examined every other day after the commencement of chemotherapy. Antibiotics and G-CSF could be used when grade 4 CIL occurred. Chemotherapy delayed until the WBC≥3.0×10^9/L in patients whose WBC<3.0×10^9/L.

Dose intensity of chemotherapy

For every patient and every drug received, actual dose intensity was calculated as the ratio between total dose received and total time on treatment (defined as the interval between date of first chemotherapy (day 1 of cycle one) and date of the end of the last cycle (day 21). Relative dose intensity of every drug was calculated as the ratio between actual dose intensity and the planned dose intensity. For two-drug regimens, the mean relative dose intensity was calculated. The relative dose intensity quoted in the text is the mean of the relative dose intensity of cisplatin and vinorelbine. A dose reduction was defined as a dose of less than 90% of the initial dose.

Efficacy and toxicity evaluation

Grade1, 2, 3, 4 of CIL was defined as 3.0-3.9×10^9/L, 2.0-2.9×10^9/L, 1.0-1.9 ×10^9/L, <1.0×10^9/L, respectively. Leutropenia was categorised on the basis of worst WHO grade during chemotherapy: absent (grade 0), mild (grade1-2), or severe (grade3-4). Efficacy evaluation: complete remission (CR), partial remission (PR),stable disease (SD), progressing disease (PD). It was evaluated 3 cycles, 6 cycle respectively, confirmed 4 weeks later. The outcomes studied included: overall response rates (RR), time to progression (TTP) and disease control rate (DCR). RR included patients who were recorded to have CR or PR; DCR included CR, PR and SD. TTP refers to the interval from the commence of chemotherapy to disease progression.

Statistical analysis

Groups: A: absent CIL (ACIL); B: mild CIL (MCIL);C: severe CIL (SCIL). The characteristics of these groups were compared by means of Fisher's exact test, the chi-squared test and the Mann Whitney non parametric test. TTP was calculated by the method of Kaplan-Meier and groups were compared by means of the log rank test. SPSS10.0 software was used for statistical analysis.

Results

Demographics

Patients in group A, B, C were 26 cases, 74 cases and 28 cases respectively. The baseline characteristics of patients in these groups had no significant difference (Table 1). The CIL rate was 79.7% (102/128), the severe CIL incidence rate was 21.9% (28/128). Of 102 patients with CIL, worst grade was first noted in 27 patients during the first cycle, 18 in the second cycle, 16 in the third cycle, 19 in the fourth cycle, 14 in the fifth cycle, and 8 in sixth cycle. 34 patients' CIL sustained for more than 10 days. 86 cases received all six planned cycles of chemotherapy, 42 cases received 4-5 planned cycles. The reasons for the cessation of chemotherapy include: 24 cases imaging progress, 10 cases symptoms worsen, 3 cases of pleural infection (2/3 with febrile neutropenia), 2 cases of pulmonary embolism, 2 cases abandoned the chemotherapy, 1 case of renal toxicity. The drug relative dose intensity in three groups was 0.92 (95%CI: 0.34-1.06), 0.89 (95%CI: 0.30-1.06), 0.86 (95%CI: 0.35-1.03). The dose intensity in group B and C was slightly lower, but no statistical significance. The main reason for dose intensity declining was to stop or delay treatment.

Response rates

The overall RR and DCR for all patients was 54.7%

Table 1. The Baseline Characteristics of Patients in Three Groups Had No Significant Difference

	A	B	C	P
median age	50(45, 55)	56(53, 59)	52(48, 56)	0.179
Sex				
male	18	56	16	
female	8	18	12	0.186
Performance status				
0	9	30	11	
1	16	45	17	0.887
stage				
IIIB	14	38	16	
IV	12	36	12	0.869
Bone metastases				
+	6	8	4	
-	20	66	24	0.302
Histological subtype				
Adenocarcinoma	12	42	18	
Squamous	12	28	8	
Other	2	4	2	0.714
Cycles				
6	16	50	20	
<6	10	24	8	0.737

Table 2. The Overall RR and DCR in Three Groups are Significantly Different

Groups	CR	PR	SD	PD	PR(%)	P	DCR	P	TTP(95%CI)	P
A	0	8	8	10	30.8		61.5		150(91-209)	
B	0	42	20	12	56.8		83.8		189(181-197)	
C	0	20	6	2	71.4	0.01	92.9	0.009	207(172-242)	0

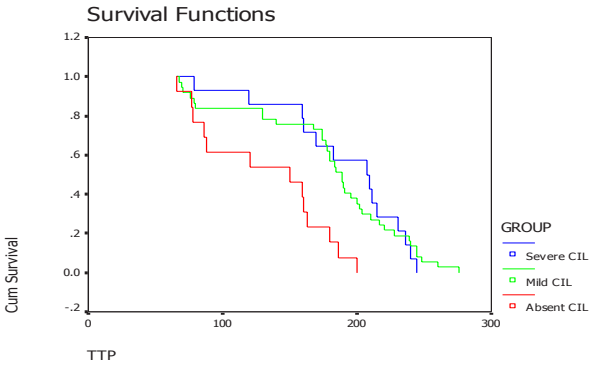

Figure 1. TTP in Three Groups were Significantly Different (p=0.000)

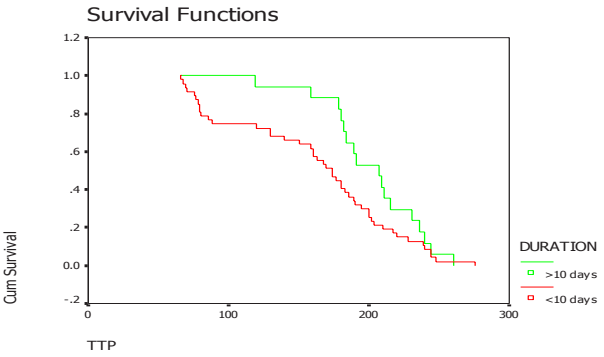

Figure 2. TTP in Patients Whose CIL Duration Time was More than 10 Days was Significantly Prolonged (p=0.0213)

(70/128) and 81.3% (104/128).The RR for A, B, C group was 30.8% (8/26), 56.8% (42/74), 71.4%(20/28), respectively (p=0.010); the DCR was 61.5% (16/26), 83.8% (62/74), 92.9% (26/28), respectively (p=0.009) (Table 2).

TTP

The TTP in group A,B,C was 150 days (95%CI: 91-209), 189 days (95%CI:181-197), 207days (95%CI: 172-242), respectively (p=0.000), (Figure 1). In patients whose CIL duration time was more than 10 days or less than 10 days ,it was 207 days (95%CI: 188-226), 174 days (95%CI: 161-187), respectively (p=0.0213) (Figure 2). Stratified analysis found that TTP was significantly prolonged in patients with mild CIL and ECOG 0 ,the median TTP was 195 days (95%CI: 177-213), the mean TTP was 206 days (95% CI: 193-218), the difference was statistically significant (p=0.0412) (Figure 3).The median TTP for IIIB and IV patients was 183 days (95%CI: 172-194) and 178 days (95%CI: 166-190), p=0.227 (Figure 4).

Discussion

CIL is the one of the major factors that limited the dose increasing of cytotoxic drugs, and jeopardising the

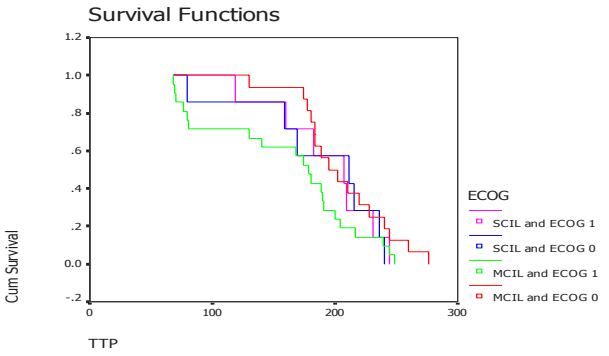

Figure 3. The Association of Performance Status on TTP. The Difference was Statistically Significant (p=0.0412)

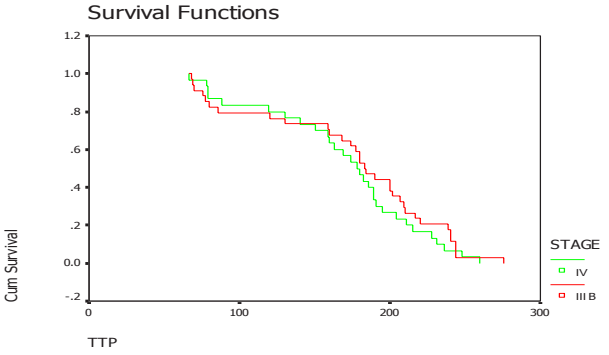

Figure 4. TTP in Patients of IIIB and IV Stage was Similar (p=0.227)

outcomes of chemotherapy. In general, the outcomes of chemotherapy is depended largely on the two factors (Kvinnsland 1999; Di Maio et al., 2005), a sufficient amount of active drug reaching to the target and whether the target is sensitive to the drug. These factors also apply to healthy cells, particularly haemopoietic cells. The availability of active drug at tumor cells or healthy cells is affected by pharmacokinetic factors (ie, the metabolism, distribution, and catabolism) of drugs, which produce a similar effect in tumor cells and healthy cells. The sensitivity of tumor cells and healthy cells is affected, in part, by genetic predisposition, which can similarly affect both cell types, but is also modified by tumor-specific acquired resistance. The sensitivity of chemotherapy drugs is impacted by individual genetic polymorphisms. It is relatively higher in patients experiencing CIL, at the same time it also shows that there are sufficent drugs reaching to the tumor cells, so got better efficacy (Kvinnsland, 1999; Banerji et al., 2006). Patients without CIL did not meet the biological effective dose although it was calculated in accordance with the body surface area (Cameron et al., 2003; Di Maio et al., 2005; Banerji et al., 2006),and poorer treatment outcomes were got. So some scholars indicated that the dose of drugs could be adjusted in accordance with toxicity (Sawyer and Ratain., 2001; Singh 2005; Massimo et al., 2006), that is, toxicity-adjusted dose (TAD).Those

drugs that bone marrow are the major dose-limiting toxicity could be optimized according to CIL to realize dosage individualization to get better outcomes. Modest reductions in dose intensity and drug-induced neutropenia have no major impact on survival of patients (Brunetto et al., 2010).

Previous studies have revealed the association of CIL on treatment outcomes of chemotherapy. Saarto (Saarto et al., 1997) found the same trend in his study that patients with stage II/III breast cancer would have a longer distant disease-free survival and overall survival if they experienced CIL during chemotherapy. Poikonen (Poikonen et al., 1999) and his colleagues then reported the result of a systematic study in 1999. They presumed that a low leucocyte nadir during the adjuvant CMF chemotherapy is associated with favorable DDFS and it may be a useful biological marker for chemotherapy. The DDFS of 99 cases with CIL which sustained 9-14 days was longer (RR:1.56, p=0.005). In this year, a recently study was done by Han Y. Early breast cancer patients in there hospital were reviewed. Three hundred and thirty-five patients who had been treated with six cycles of cyclophosphamide, epirubicin, and fluorouracil (CEF) were studied. The association between chemotherapy-induced neutropenia and overall survival (OS) was assessed. According to a multivariate Cox model with time-varying covariates, hazard ratios of death were 0.434 (95% confidence interval (CI), 0.298-0.634; P < 0.001) for patients with mild neutropenia, and 0.640 (95% CI, 0.42-0.975; P = 0.038) for those with severe neutropenia. They concluded that neutropenia occurring in early breast cancer patients was an independent predictor of increased survival, and neutropenia in patients who receive chemotherapy is strongly associated with a better prognosis. Japanese experts (Banerji et al., 2006) investigated the association of chemotherapy induced leutropenia on treatment outcomes in small cell lung cancer in 2006.Patients were stratified into two groups (A) those experiencing grades 0-2 neutropenia and group (B) those experiencing grades3-4 neutropenia. The median TTP in groups A and B was 30 and 38 weeks, p=0.05. The median OS in groups A and B was 47 weeks versus 60 weeks, p=0.008.The differences in TTP and OS were not significant in patients with extensive stage disease. The results indicated that Occurrence of chemotherapy induced grade 3 or 4 neutropenia correlated with OS in patients with SCLC receiving carboplatin and etoposide chemotherapy. The association of CIL on treatment outcomes of chemotherapy was also found in some other malignancies, such as osteosarcoma (Ratain, 1998), ovarian cancer (Sawyer and Ratain., 2001).

Retrospective studies on advanced NSCLC have done previously. Di Maio et al. (2005) performed a pooled analysis of three randomised trials. 1265 patients who received chemotherapy (vinorelbine, gemcitabine, gemcitabine and vinorelbine, cisplatin and vinorelbine, or cisplatin and gemcitabine) within three random trials was analyzed. Primary landmark analyses were restricted to 436 patients who received all six planned chemotherapy cycles and who were alive 180 days after randomisation. Neutropenia was categorised on the basis of worst WHO grade during chemotherapy: absent (grade 0), mild (grade1-2), or severe (grade3-4). All statistical analyses were stratified by treatment allocation. Analyses were repeated in the out-of-landmark group (829 patients), stratifying by treatment allocation and number of chemotherapy cycles. The primary endpoint was overall survival. They found that, in the landmark group, hazard ratios of death were 0.65 (0.46–0.93) for patients with severe neutropenia and 0.74 (0.56–0.98) for those with mild neutropenia. Median survival after the landmark time of 180 days was 31.4 weeks (95%CI: 25.7–39.6) for patients without neutropenia compared with 42.0 weeks (32.7–59.7) for patients with severe neutropenia, and with 43.7 weeks (36.6–66.0) for those with mild neutropenia (severe vs mild vs no neutropenia p=0.0118). Findings were much the same for the out-of-landmark group. According to these results, Di Maio and his colleagues concluded that, neutropenia during chemotherapy is associated with increased survival of patients with advanced non-small-cell lung cancer, and its absence might be a result of underdosing. Another study was done in 2006 by Camps and his colleagues (Camps et al., 2006). They analyzed data of 493 patients who received chemotherapy (cisplatin and docetaxel) within the pharmacogenomic, open-label, single-arm, multicentric PLATAX trial. Three subgroups of patients were considered: global population, patients who received at least 3 cycles of chemotherapy, and those who received at least 6 cycles. Neutropenia was categorised on the basis of worst WHO grade during chemotherapy. Relative dose intensity was analyzed for both drugs. The primary endpoint was overall survival. They found that median OS was 9 months (8.2-9.7). Median relative dose intensity was 0.97 for cisplatin and docetaxel. 403 patients received at least 3 cycles of chemotherapy, and 255 received 6 or more. Neutropenia appeared in 172 patients (30.8%), 72 of them G3-4 (18.6%). Dose intensity was lower in patients who presented any grade of neutropenia versus those without neutropenia in the three analyzed subgroups, for both drugs (p<0.05). Factors associated with higher risk of death were ECOG 1-2 (HR 1.8, p = 0.00) and female (HR 1.5, p = 0.02). There were no differences in overall survival between patients with G0 vs G1-2 vs G3-4 neutropenia (8.7 vs 11.6 vs 9.6 m, p=0.41), however the risk of death was lower in patients with ECOG 0, that presented neutropenia (HR: 0.545, 95%CI: 0.31, 0.96; p=0.034). Camps concluded that neutropenia during chemotherapy may be associated with increased survival of patients with advanced non-small cell lung cancer and ECOG 0. Its absence is not a result of underdosing. The recent study was done in 2009 by Kishida Y. A total of 387 chemotherapy-naïve patients who received chemotherapy (vinorelbine and gemcitabine followed by docetaxel, or paclitaxel and carboplatin) in a random controlled trial were evaluated. The adjusted hazard ratios for patients with grade-1 to 2 neutropenia or grade-3 to 4 neutropenia compared with no neutropenia were 0.59 (95% confidence interval (CI), 0.36-0.97) and 0.71 (95% CI, 0.49-1.03), respectively. The hazard ratios did not differ significantly between the patients who developed neutropenia with stable disease (SD), and those who

lacked neutropenia with partial response (PR). Kishida Y and his colleagues concluded that, chemotherapy-induced neutropenia was a predictor of better survival for patients with advanced NSCLC. Prospective random trials of early-dose increases guided by chemotherapy-induced toxicities were warranted.

We designed this prospective study in order to explore the association of CIL on treatment outcomes in advanced NSCLC.128 patients with advanced NSCLC was selected. CIL rate was 79.7%, severe CIL rate was 21.9%.The differences of RR and DCR in three groups were statistically signify -cant, so as TTP. The TTP was significantly longer in patients whose CIL sustaining for more than 10 days or with mild CIL and ECOG 0.Patients with CIL did not receive higher dose intensity of chemotherapy drugs. Our study indicated that CIL could be a biological measure of drug activity and a marker of efficacy. Dose adjusting could be done according to CIL in order to individualize cytotoxic chemotherapy. Further observation was needed to assess whether patients with CIL have a favorable OS.

Acknowledgements

The author(s) declare that they have no competing interests.

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