RESEARCH ARTICLE

Docetaxel and Cisplatin in First Line Treatment of Patients with Unknown Primary Cancer: A Multicenter Study of the Anatolian Society of Medical Oncology

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Abstract

Background: The overall prognosis for cancers of unknown primary (CUP) is poor, median overall survival (OS) being 6-12 months. We evaluated our multicentric retrospective experience for CUP administered docetaxel and cisplatin combination therapy. Materials and Methods: A total of 29 patients that were pathologically confirmed subtypes of CUP were included in the study. The combination of docetaxel (75 mg/m², day 1) and cisplatin (75 mg/m², day 1) was performed as a first line regimen every 21 days. Results: The median age was 51 (range: 27-68). Some 17 patients had multimetastatic disease on the inital diagnosis. Histopathological diagnoses were well-moderate differentiated adenocarcinoma (51.7%), undifferentiated carcinoma (27.6%), squamous cell cancer (13.8%), mucoepidermoid carcinoma (3.4%) and neuroendocrine differentiated carcinoma (3.4%). Median number of cycles was 3 (range: 1-6). Objective response rate was 37.9% and clinical benefit was 58.6%. Median progression free survival (PFS) and overall survival (OS) were 6 months (range: 4.3-7.7 months) and 16 months (range: 8.1-30.9 months), respectively. Fourteen patients (60.8%) were treated in a second line setting. There was no treatment related death. Most common toxicities were nausia-vomiting (44.6%) and fatigue (34.7%), serious cases (grade 3/4) suffering nausia-vomiting (10.3%), neutropenia (13.8%) and febrile neutropenia (n=1). Conclusion: The combination of cisplatin and docetaxel is an effective regimen for selected patients with CUP.

Keywords: Cancer of unknown primary - docetaxel - cisplatin - combination - clinical benefit

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Introduction

Cancer of unknown primary (CUP) accounts for 2-10% of all malignancies and accepted as metastatic cancer (Fizzazi et al., 2011; Pavlidis et al., 2012; Greco et al., 2012). Incidence of CUP is decreased secondary to advances of pathology and imaging methods (Greco et al., 2012; Hemminki et al., 2012). In many patients, pathologic diagnosis is adenocarcinoma and the disease is on the multimetastatic sites. Except selected patients, survival benefit of the treatments are limited and the intent of treatment is palliative. The prognosis of CUP is poor, response rate (RR) is 20-35%, median overall survival (OS) is 6-12 months and one year OS is 15-35% (Fizzazi et al., 2011; Greco et al., 2012; Pavlidis et al., 2012). Although different chemotherapy regimens were evaluated, there is no standard treatment, currently. Platin based regimens are mostly used and the results of phase II taxane studies are promising in patients with CUP (Poussel et al., 2004; Adenis et al., 2010; Hainsworth et al., 2010). Here-in, we evaluated our multicentric retrospective experience for CUP administering docetaxel and cisplatin in combination therapy.

Materials and Methods

Between 2007 and 2010, totally 29 patients that were pathologically confirmed subtypes of CUP was evaluated in the five institutions, retrospectively. The treatment naive patient has pathologically confirmed CUP and although detailed examinations (physical examination, chest graphy, thoraco-abdominal computarized tomography (CT), mammography, if necessary pozitron emission tomography/ computarized tomography- PET/CT) and diagnostic sample, the primary was unable to identify. Female patient with alone axillary lymph node

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involvement and adenocarcinoma of the peritoneal cavity, midline carcinoma that suspected with germ cell tumor and patient with SCC at single site involvement were not included the study.

The patients were treated with the combination of docetaxel (75 mg/m^2, day 1) and cisplatin (75 mg/m^2, day 1) every 21 days. The evaluation for the treatment response in CUP was assessed by both clinical and radiological criteria using Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer et al., 2009). Toxicities were recorded based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Data were expressed with median values with range. While progression free survival (PFS) is defined from the initial day of treatment to first progression, OS is defined from the initial of treatment to last control or death. All statistical analyses were based on 'intent to treat'. The Kaplan Meier survival estimates were calculated. Survival curve were compared with logrank test. A p-value was accepted statistically significant if the value less than 0.05. SPSS 15 was used for statistical analysis.

Results

The median age of four female (13.8%) and 25 male (86.2%) totally 29 patients was 51 (range: 27-68). Performance status (PS) were based on World Health Organization (WHO); 0 in 6 patients, 1 in 18 patients, and 2 in 5 patients. While histopathological samples were achived from brain (n=7), bone (n=7), lymphadenopathy (n=6), liver (n=4), lung (n=3), in one patient from soft tissue metastasis and in one patient from intraabdominal metastasis. In 17 patients (58.6%) had multimetastatic (more than two different sites) disease on the initial diagnosis. Brain metastasis was detected in 8 (27.6%) of all patients and they were treated with cranial radiotherapy. Liver metastasis was detected in 5 (17.2%) of all patients. Histopathological diagnoses were; well-moderate differantiated adenocarcinoma (n=15, 51.7%), undifferantiated carcinoma (n=8, 27.6%), SCC (n=4, 13.8%), mucoepidermoid carcinoma (n=1, 3.4%) and neuroendocrine differantiated cancer (n=1, 3.4%) (Table 1).

Table 1. Patient Characteristics

		n	%
Age		51	range, 27-68
Sex	Male	25	86.2
	Female	4	13.8
PS	0-1	24	82.8
	2	5	17.2
Histology	Well-moderate diff. adenocarcinoma	15	51.7
	Undiff. carcinoma	8	27.6
	Squomous cell carcinoma	4	13.8
	Mucoepidermoid	1	3.4
	Neuorendocrine diff.	1	3.4
Multimetastatic patients		17	58.6
Metastases site	Liver	5	17.2
	Lung	3	10.9
	Brain	8	27.6
PFS, months		6	range, 4.3-7.7
OS, months		16	range, 8.1-30.9

*PS: performance status; diff: differantiated; PFS: progression free survival; OS: overall survival

Table 2. Toxicities

	Grade 1/2 (%)	Grade 3/4 (%)
Nausue-vomiting	10 (34.4)	3 (10.2)
Fatigue	5 (17.2)	4 (13.7)
Neutropenia	7 (24.1)	4 (13.7)
Febrile neutropenia		1 (3.4)
Trombocytopenia	2 (6.9)	-
Anemia	2 (6.9)	2 (6.9)
Renal toxicity	6 (20.4)	-
Diarrhaea	3 (10.2)	-

Table 3. Univariate Log Rank Testing

	PFS, p value	OS, p value
Male vs female	0.1	0.29
<65 *vs* ≥65	0.81	0.94
Performance status (0-1 *vs* 2-4)	0.13	0.27
Single *vs* multiple, metastatic sites	0.59	0.78

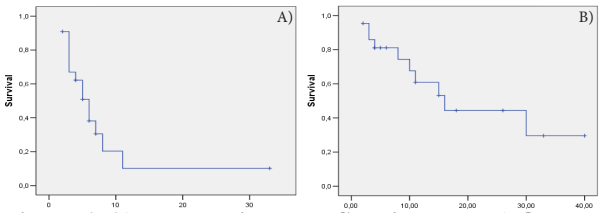

Figure 1. A) Progression Free Survival and B) Overall Survival by Kaplan-Meier

Twenty-nine patients who were treated with docetaxel and cisplatin combination at least one cycle as a first line setting of in the patients with CUP, median number of cycle was 3 (range: 1-6). There was no complete response. Although objective response rate (ORR) was 37.9% (n=11), clinical benefit was 58.6% (partial response (n=11), stable disease (n=6). Median PFS and OS were detected 6 months (range: 4.3-7.7 months) and 16 months (range: 8.1-30.9 months) respectively (Figure 1, 2). Totally 14 patients (60.8%) were treated on second line setting; regimens were gemcitabine and its combination (n=7), oral etoposide (n=3) and others (n=3). There was no treatment related death and unexpected toxicity. Dose reduction and treatment discontinuation were performed in two patients because of serious toxicities. The treatment well tolerated in generally. Although most common toxicities were nausue-vomiting (n=13, 44.8%) and fatigue (n=9, 314%), serious toxicities (grade 3/4) were nausue-vomiting (n=3, 10.3%), neutropenia (n=4, 13.8%) and febrile neutropenia (n=1) (Table 2). In univariate log rank analysis, sex, age, PS and number of metastatic sites were no independent prognostic factors for PFS and OS (Table 3).

Discussion

CUP are heterogeneous group of disease that characterised poor prognosis and short treatment response duration. There is no clear standard treatment approach (Fizzazi et al., 2011; Pavlidis et al., 2012). Although RR and median OS were 10% and 4 months with single agent 5 fluorouracil, doublet regimen that contain third generation cytotoxic agents (taxane, gemcitabine) were achieved higher RR and one year OS 30-40% and 50% respectively

(Briasoulos et al., 2000; Greco et al., 2001; Golfinopoulos et al., 2009; Massard et al., 2011). The combination of taxane and platin is synergistic and well tolerated in many solid tumor and also evaluated in patients with CUP (Greco et al., 2000a; Greco et al., 2000b; Lazaridis et al., 2008; Mukai et al., 2010; Nishimori et al., 2010; Yakushiji et al., 2010). In the present study, median PFS (6 months) and median OS (16 months) were comparable with the previous reports (Greco et al., 2000; Nishimori et al., 2010; Yakushiji et al., 2010).

In a prospective phase II study, combination of docetaxel and either cisplatin or carboplatin, 90% of the patients were adenocarcinoma and undifferantiated histology and majority were multimetastatic. In docetaxel-cisplatin arm, 26% of the patients showed major response and median OS and one year OS were 8 months and 42% respectively. In 7 patients treatment discontinued because of grade 3/4 gastrointestinal toxicities (Mukai et al., 2010). A study evaluated different doses of the combination of docetaxel (60mg/m^2/d) and cisplatin (80 mg/m^2/d). The median age was 56.5 years of 45 patients and 14 patients (33%) had visceral disease. The overall response rate was 65.1%. The median time to progression and median OS were 5.0 months and 11.8 months. However there is no differences in terms of OS and RR with present study (Lazaridis et al., 2008). While median age and PS of the patients similar to present study, 60% of the patients with presented with lymph node metastases. RR (58.6% *vs* 65%) and PFS (6 months *vs* 5 months) are similar however OS was superior (16 months *vs* 11.8 months) in our study. The result may explained with our patients were treated with more second line treatment on progression and low incidence of liver involvement. An overall response rate of 62.5% was seen in Japanese patients with CUP who were treated same combination. The RR and survival were superior than present study. The median DFS and OS were 8.7 months and 22.7 months respectively (Yakushiji et al., 2010). Another trial had a response rate of 57.1% and the median OS was 13.2 months with same combination (Greco et al., 2000).

CUP are classified to pathologically; well-moderate differantiated adenocarcinoma (60%), undifferantiated carcinoma (30%), SCC (5%) and undifferantiated tumors (5%) (Fizzazi et al., 2011; Pavlidis et al., 2012). In our study population were mostly adenocarcinoma and undifferantiated carcinoma, only minority subset (13.8%) were SCC. Notably patients had brain metastases (27.6%) and multimetastatic involvement (58.6%) this maybe explain with the characteristics of the hospitals where they are referred. Most of patients were good PS (0-1; 82.8%). The prognosis of metastatic especially extranodal metastatic patients is worse unfortunately this group consist of 80-85% of all CUP ((Fizzazi et al., 2011; Greco et al., 2012a; Greco et al., 2012b; Pavlidis et al., 2012). Recent study that has the patients mostly adenocarcinoma, showed that lymph node metastatic patients has better outcome compare to visceral involvement; median OS was 8 months vs 3 months and one year OS were 41% vs 17%, respectively (Greco et al., 2012). In a recent study evaluated to 49 patients with liver metastatic CUP, similar to our patients that majority male and adenocarcinoma histology. In this study 62% of the patients multimetastatic thus the study results, ORR and median OS were 12% and 10 months respectively, were inferior than our results. Age and extrahepatic disease were detected as a prognostic factor (Culine et al., 2002). Another study, median age was 67 and 64.5% of the patients with multimetastatic CUP. Median OS and 1 year OS were 2.5 months and 24.5% (Lazaridis et al., 2008).

In present study there was no treatment related death. Although the treatment generally well tolerated, most common toxicities were nonhematological. Serious toxicities were low reported in present study because of retrospective nature. In previous studies, serious hematological toxicities (12-17%) and non-hematological (3-30%) were reported and there were no toxic death (Fernandez-Cotarelo et al., 2010; Hainsworth et al., 2010). There are several prognostic factors such as multiple metastatic sites, liver metastasis, elevated lactate dehydrogenase level (Culine et al., 2002; Seve et al., 2006). However there is no effect sex, age, PS and number of metastatic sites on survival in present study. The study drawbacks are retrospective nature, limited sample size and lack of quality of life evaluation.

Most of the patients with CUP have unfavourable prognosis and treatment of patient with CUP is designed histopathologic and clinical features of individual. Combination of cisplatin and docetaxel is a valuable option for selected patients with CUP

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