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ORIGINAL ARTICLE

Chemotherapy in carcinomas of unknown primary site

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Summary

Purpose: *Carcinomas of unknown primary site (CUPS) are highly malignant diseases with a usually ominous prognosis. We report on the efficacy of chemotherapy in the treatment and survival of patients with CUPS.*

Patients and methods: *The study involved 63 patients with metastatic CUPS. Following routine light microscopy, the histological findings were classified into 3 groups: squamous cell carcinoma - 8 patients; adenocarcinoma - 33 patients; and undifferentiated carcinoma - 22 patients. Combination chemotherapy with doxorubicin 50 mg/m² (day 1), cisplatin 60 mg/m² (day 1), and etoposide 120 mg/m²/day (days 1-3) every 3 weeks was administered to 32 patients (20 females and 12 males), aged 29-70 years (median 54 years) who met the inclusion criteria. All patients with stable disease (SD), partial response (PR) or complete response (CR) received 6 cycles of chemotherapy.*

Results: *CR was achieved in 3 (9.4%), PR in 12 (37.5%), and SD in 10 (31.2%) patients. Seven (21.9%) patients had progressive disease (PD). The overall response rate (RR) was 46.9% (15/32) and the median response duration of CR+PR was 11 months (range 4-43⁺ months). The overall survival (OS) of patients treated with chemotherapy (n=32; 50.8%) was better compared with the OS of those not receiving chemotherapy (n=31; 49.2%; p <0.01). Also the 2-year survival of patients with chemotherapy (40%) and without chemotherapy (0%) implies potential curability in a specific subset of these patients.*

Conclusion: *The usage of the aforementioned doses and chemotherapy scheme appears to improve the outcome of patients with carcinoma of unknown primary site.*

Key words: cancer, chemotherapy, survival, unknown primary site

Introduction

CUPS comprise a group of heterogenous tumours that share unique clinical characteristics of a metastatic disease with no identifiable origin at the time of diagnosis. The primary site is supposed to either have a slow growth or even become involute. Despite the obvious advances in tumour imaging and pathology, patients with CUPS make up approximately 10% of the general oncologist's practice [1]. CUPS is a metastatic malignancy with its source remaining unknown even after a good history, physical examination, chest X-ray, and abdominal and pelvic computed tomography (CT) scan have been done. The dilemma for the oncologist is to determine how much diagnostic work-up is appropriate. The reason to know the origin of the tumour is to allow for a chemotherapy tailored to each particular tumour. Optimal chemotherapy remains to be determined, and the benefits of chemotherapy over best supportive care are still unclear [2]. Durable responses with platinum-based chemotherapy have been reported only in the subset of patients with poorly differentiated carcinomas with a 10-20% long-term survival [3].

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Herein we report on the efficacy of a chemotherapy policy in the management of patients with CUPS.

Patients and methods

The study included 63 patients diagnosed (or made subjects to additional diagnoses) at the Clinic of Oncology, Clinical Centre - Niš, from January 1997 to December 2000. All of the patients presented with metastatic tumours, the primary site of which could not be detected with non-invasive diagnostic procedures (clinical examination, standard hematological and biochemical analyses, tumor markers – CEA, CA 15.3, CA 19.9, CA 125, PSA, NSE, β-HCG, AFP – chest X-ray, ultrasound or CT scan of the abdomen and pelvis, and endoscopic examinations based on histological findings). Of the 63 patients, 37 (58.7%) were males and 26 (41.3%) females, aged 29-70 years (median 56 years). The characteristics of the patients are given in Table 1.

Following routine light microscopy, the histological findings were classified into 3 groups: squamous cell carcinoma - 8 (12.7%) patients; adenocarcinoma - 33 (52.4%) patients; and unclassified (undifferentiated) carcinoma - 22 (34.9%) patients (Figure 1).

The organs and tissues with metastases are shown in Table 2. Chemotherapy was administered to 32 patients (20 females and 12 males), aged 29-70 years (median 54 years), who met the following inclusion criteria: age up to 70 years; ECOG performance status 0-3; no previous chemotherapy; adequate cardiac, renal, and hepatic function; expected survival more than 2 months; metastatic disease excluding the possibility for surgical approach; presence of two-dimensional measurable and/or evaluable lesions; no central nervous system metastases.

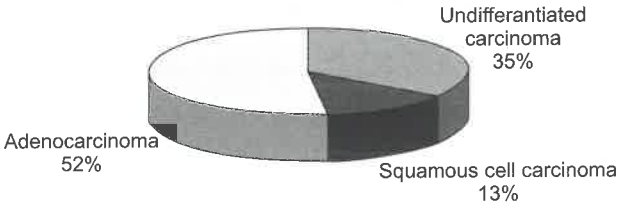


Figure 1. Prevalence of histological types in CUPS.

This group comprised 5 patients with squamous cell carcinoma, 13 patients with adenocarcinoma, and 14 patients with undifferentiated carcinoma.

Each treatment cycle included doxorubicin 50 mg/m^2 day 1, given as a bolus injection through a running tube of 500 ml saline. Then, prehydration for cisplatin with 1000 ml saline was given as 1h infusion. After 1h

Table 1. Patient characteristics

Characteristic	*Patients n (%)*
Age (years), median (range)	56 (29-72)
ECOG performance status	
0	4 (6.3)
1	16 (25.4)
2	19 (30.2)
3	17 (27.0)
4	7 (11.1)
Sites of metastases	
Liver, peritoneum, retroperitoneum	31 (49.2)
Lungs, mediastinum, pleura	29 (46.0)
Supradiaphragmatic lymph nodes	24 (38.1)
Infradiaphragmatic lymph nodes	15 (23.8)
Bones, soft tissues	19 (30.2)
Number of metastatic sites	
1	15 (23.8)
2	22 (34.9)
>2	26 (41.3)

Table 2. Organs and tissues with metastases

Organ/tissue	*Patients n (%)*
Lungs	25 (39.68)
Cervical lymph nodes	24 (38.09)
Liver	18 (28.57)
Retroperitoneal lymph nodes	17 (26.98)
Bones	16 (25.39)
Inguinal lymph nodes	14 (22.22)
Axillary lymph nodes	11 (17.46)
Peritoneum	8 (12.69)
Skin nodes	4 (6.35)
Bone marrow	3 (4.76)
Soft tissues	3 (4.76)
Pleura	2 (3.17)
Mediastinal lymph nodes	2 (3.17)
Brain	1 (1.58)
Adrenal	1 (1.58)
Testis	1 (1.58)

infusion of 500 ml mannitol 10%, cisplatin 60 mg/m^2 was administered in 1000 ml saline in 1h infusion. An additional 2 litres of saline were infused over the next 4 hours. Supplementation with potassium chloride and magnesium sulfate or magnesium chloride might be necessary. Etoposide was given in 500 ml saline over 1h period at a dose of 120 mg/m^2 daily on days 1-5. Premedication prior to chemotherapy was given consisting of dexamethasone 20mg i.m. and the administration of a 5HT3 receptor antagonist (ondansetron 8-16 mg as a i.v. infusion in 250 ml saline). The intercycle interval was 3 weeks. All patients with SD, PR or CR received 6 cycles of chemotherapy.

CR required complete disappearance of all clinically and radiographically detectable disease for at least 4 weeks. PR required at least a 50% reduction in the size of all measurable lesions as measured by the product of the greatest perpendicular diameters, with no appearance of new lesions. SD was defined as a reduction of <50% or increase of <25% of the measurable disease, without appearance of new lesions. PD was defined as an increase of >25% in the size of any existing measurable lesion or the appearance of any new lesion.

Response duration was defined as the period when an objective response was first documented until the appearance of SD or PD. Toxic effects were graded according to the WHO toxicity criteria.

The obtained results were analyzed according to the methods of descriptive and analytic statistics. Survival analysis was done according to Kaplan-Meier life-table method [4], using the log rank test for the comparison of two or more factors [5].

Results

CR was achieved in 3 (9.4%) patients, PR in 12 (37.5%) patients, SD in 10 (31.2%) patients, and PD in 7 (21.9%) patients. The overall RR was 46.9% (15/32, Figure 2).

Response duration of the 3 CR patients was 43$^+$, 18 and 7 months. Response duration of PR patients ranged between 4-29 months (median 8 months). The median response duration of CR+PR patients was 11 months (range 4-43$^+$). The probability for a patient from this group to survive 24 months was 0.397 (Figure 3).

Thirty-seven patients died during the 44-month observation period, while 26 patients were alive.

The average survival time of the entire group of 61 patients was 17.89 months (95% CI 12.96-22.83), and the median was 10.00 months (95% CI 2.95-17.05). The probability for a patient to survive in the following 24 months was 0.228.

Of 31 patients not treated with chemotherapy, 25 (80.65%) died during the observation period. The average survival time was 7.11 months (95% CI 5.27-8.94), and the median survival time was 5 months (95% CI 3.92-8.94). The probability for a patient from this group to survive in the following 10 months was 0.166 (Figure 3).

In the group of 32 patients with chemotherapy, 12 (37.5%) died during the observation period. The average survival time was 26.6 months (95% CI 19.5-33.7), and the median survival time was 22.0 months (95% CI 14.3-29.7). The difference in survival between treated and not treated patients was statistically significant (p <0.001, Figure 3).

Comparative analysis of the OS in relation to response to chemotherapy showed a clear benefit of patients achieving CR and PR (Table 3, Figure 4).

Hematological toxicity was generally moderate. WHO grade 3-4 neutropenia was encountered in 37.5% of the cycles. Febrile neutropenia was noted in 10.6%

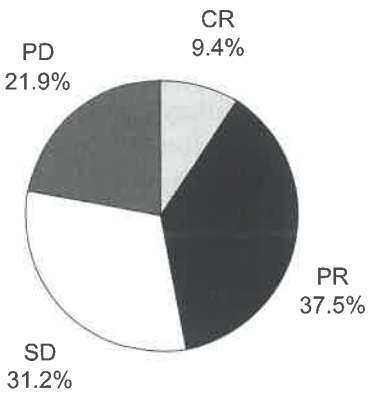


Figure 2. Response to chemotherapy.

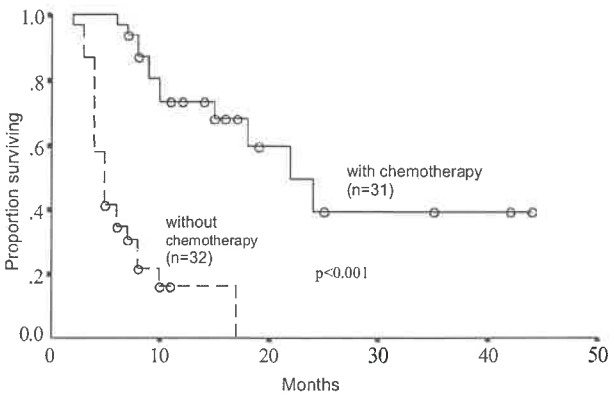


Figure 3. Survival of patients with and without chemotherapy.

Table 3. Differences in overall survival in relation to response to chemotherapy

	CR+PR	*SD+PD*	*p-value*
Deaths/total number of patients	2/15 (13.3%)	10/17 (58.8%)	0.0005
Average survival (months)	36.51 (95% CI 27.8-45.2)	14.85 (95% CI 10.8-18.9)	

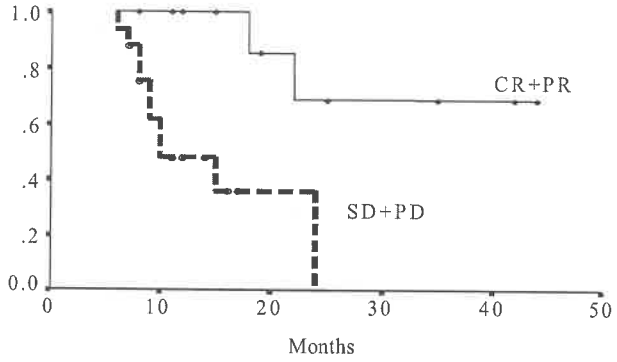


Figure 4. Overall survival according to response to chemotherapy.

of the cycles given and was successfully treated with antibiotics and GCSF support. No patient developed WHO grade 3-4 neurotoxicity or nephrotoxicity. Severe nausea and vomiting (WHO grade 3-4) were registered in 31.2% of the patients or in 24.6% of the cycles administered. Grade 3 alopecia was observed in 34.3%, and grade 3 cardiotoxicity in 6.2% of the patients. No treatment-related deaths occurred.

Discussion

The survival of the examined group of patients generally coincides with the results reported by other authors. The median survival of 10.00 months for the entire group with probability of a 24-month survival in 22.8% patients corresponds to the results by Altman and Cadman [6], and, in particular, by Hess et al. [7], and is better than the results obtained by Junginger and Hoeffken [8].

A significantly better survival was registered in patients receiving chemotherapy ($p < 0.001$). A plateau of considerable time length in the survival curve of patients achieving CR and PR suggests potential curability in a specific subset of these patients.

A significantly better survival of the patients treated with chemotherapy was expected, since chemotherapy was given only to those patients who met the inclusion criteria, i.e. those having better prognosis.

The overall survival of patients treated with chemotherapy varies in different studies, depending on the patient characteristics and does not appear to exclusively depend on the chemotherapy type administered. Therefore, unsatisfactory results are reported in the group of patients with adenocarcinoma of unknown primary site treated with CFT (cisplatin-5-FU-tamoxifen) [9]. The results are not surprising, as these patients are most unrewarding for treatment since this cancer category is characterized by chemoresistance. In this study, the median OS was only 121 days. Culine et al. reported a median OS of 11 and 8 months with "high-dose" chemotherapy, depending on the characteristics of patients and protocols [10]. Greco et al. reported a median OS of 8 months with docetaxel, and 13 months with paclitaxel [11]. In recent studies, the subset of patients with good prognosis and a good response to chemotherapy is excluded and the type of therapy is well defined. In some of the earlier studies in patients with poorly differentiated carcinoma and poorly differentiated adenocarcinoma, a 12% survival longer than 6 years is reported (median 11 years) [3,12,13]. Therefore, the survival in the chemotherapy group in our study is better compared to the studies that exclude the group with favourable prognosis.

A comparatively better response to chemotherapy administered could be explained by the fact that this group also includes patients belonging to the subset of clinical cases known for having a better prognosis and for receiving a specific well-defined treatment. This subset of patients (prognostically favorable group) comprises women with adenocarcinomas that affect only the axillary lymph nodes or only the lymph nodes of the peritoneal cavity; patients with squamous cell carcinomas affecting only the cervical or only the inguinal lymph nodes; patients with carcinoma of the "midline", who are highly suspicious for germ cell tumours [14, 15]. In this study, 5 female patients had adenocarcinoma with retroperitoneal lymph nodes, of whom 3 also had positive inguinal lymph nodes and 2 had peritoneal carcinomatosis. One woman responded with CR of the disease, 2 had PR, and 2 showed PD. One CR was achieved in a wom-

an with inguinal and retroperitoneal lymph nodes, but this was a case of anaplastic tumour. One patient had a "midline" tumour with an increased level of beta human chorionic gonadotropin (β-HCG; 77 IU/ml) and a CR to chemotherapy. In one female and one male patient, metastatic nodes developed (in the neck and inguinal region, respectively) in a bulky form, whilst in both cases SD was achieved.

Unfortunately, the majority of patients with CUPS do not belong to a prognostically favourable subset and are patients with adenocarcinomas responding poorly to chemotherapy [16].

The best results were taken with cisplatin-based chemotherapy. Poorly differentiated neuroendocrine carcinomas or adenocarcinomas located in the retroperitoneum and peripheral lymph nodes are particularly well responsive to this therapy [3]. It should be noted that the chemotherapy used in our study did contain cisplatin in combination with doxorubicin and etoposide. It is of particular significance that cisplatin and etoposide should be combined due to these two agents' synergism [17].

The strategy of high dose intensity is currently not fully accepted and requires additional research [10].

Promising results have been recently reported with newer agents, such as paclitaxel, docetaxel, CPT 11, and gemcitabine. Paclitaxel combined with carboplatin and etoposide per os has shown a RR of 47% with 13% CR. Due to low toxicity, high effectiveness and a median survival of 13.4 months, this protocol has been recommended as a standard initial therapy for patients with CUPS [15]. Similar results were reported in the study by Greco et al., using docetaxel and carboplatin [11]. However, it still remains as the best option to include these patients in controlled prospective clinical trials [17]. In a two-arm prospective randomized study by Kreačić et al., a combination of doxorubicin 50 mg/m^2 day 1, cisplatin 60 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1-3 was used in the first arm, whilst the second arm received mitoxantrone (12 mg/m^2 on the first day) instead of doxorubicin [16]. Comparable results were obtained with a slightly lower RR (32% and 34.5%, respectively) compared to our patients treated with chemotherapy, which was the consequence of excluding patients from "a prognostically favourable group".

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