The purpose of this study was to investigate the treatable subsets in cancer of unknown primary origin (CUP). Fifty patients (27 males and 23 females; median age, 53 years) with CUP diagnosed between April 1992 and June 1999 were analyzed retrospectively. Of the 50 patients, 39 received chemotherapy: platinum-based in 31, non-platinum-based in 4, and clinical trials of new agents in 4. Of the 39 patients, 13 (33.3%; 95% confidence interval: 19.1–50.2%) showed objective responses, with 4 complete responders. Patients with poorly differentiated carcinomas in whom β-subunit of human chorionic gonadotropin (β-HCG) was elevated more than 10 mIU/ml and female patients with peritoneal adenocarcinomatosis achieved high response rates (83.3% and 80%, respectively) with platinum-based chemotherapy, as compared with only a 15.3% response rate in the remaining patients. Platinum-based chemotherapy provided promising results in patients with poorly differentiated carcinomas and in female patients with peritoneal adenocarcinomatosis.

Significantly elevated serum levels of β-HCG in patients with poorly differentiated carcinoma might predict a better response to platinum-based chemotherapy. However, the investigation of novel chemotherapeutic approaches is warranted for other groups of patients with CUP.

Key words: Cancer of unknown primary — Chemotherapy — Chemosensitive subgroups — β-HCG

PATIENTS AND METHODS

Patients (n=71) were referred to the National Cancer Center Hospital East with suspected CUP between April 1992 and June 1999. All patients were diagnosed as having metastatic carcinomas, with histological or cytological confirmation. To detect the primary site, diagnostic procedures included a complete history, physical examination, chest radiographs, computed tomography (CT) of the chest, abdomen, and pelvis, endoscopic studies of the gastro-intestinal tract, and serum tumor markers, including prostate-specific antigen, α-fetoprotein (AFP), and the β-subunit of human chorionic gonadotropin (β-HCG). Immunoperoxidase staining was additionally performed, using the avidin-biotin peroxidase complex technique to detect cytokeratin, vimentin, leukocyte common antigen, β-HCG, AFP, placental-like alkaline phosphatase, neuroendocrine markers, such as neuron-specific enolase and chromogranin, and melanoma markers, such as S-100 and Hmb-45. For patients with adenocarcinomas, staining with prostate-specific antigen (PSA) and thyroglobulin was added when clinically indicated. Slides were then examined and interpreted according to current recommendations.

After the initial imaging evaluation, the primary site was identified in 16 patients: lung in 6 patients, ovary in 3, gallbladder in 2, pancreas in 2, colon in 1, stomach in 1, and esophagus in 1. By pathological evaluation, including immunoperoxidase studies, diagnoses of germ cell tumors...
Treatable Subsets in Cancer of Unknown Primary

were made in 3 patients, non-Hodgkin’s lymphoma in 1, and neuroendocrine carcinoma in 1. The remaining 50 patients were analyzed in this study.

Because there is no standard therapy for CUP, chemotherapy agents were selected on the bases of case conferences. Patients gave informed consent for the treatment. In general, strategies of chemotherapy were as follows: (1) a combination of cisplatin and etoposide with or without bleomycin for patients with poorly differentiated carcinoma primarily involving midline structures; (2) a combination of cyclophosphamide, doxorubicin, and cisplatin, or carboplatin and cyclophosphamide for female patients with elevated CA 125; and (3) a combination of cyclophosphamide and doxorubicin with or without 5-fluorouracil for female patients with axillary lymph node metastasis.

Responses were defined according to World Health Organization criteria.9 Briefly, complete response (CR) was defined as the complete disappearance of all assessable lesions and signs of disease for at least 4 weeks. Partial response (PR) was defined as a reduction of 50% or more in the sum of the products of the perpendicular dimensions of measurable lesions and the appearance of no new lesion for at least 4 weeks. Stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% in the 2 greatest dimensions of measurable lesions and the appearance of no new lesions. Progressive disease (PD) was defined as any evidence of disease progression of 25% or more, or the appearance of a new lesion.

Overall survival was calculated from the first day of treatment, or from the day of admission in the case of patients managed with best comfortable care until the date of death or the date of the last follow-up. A survival curve was estimated by the Kaplan-Meier method.

RESULTS

Patient characteristics The characteristics of the 50 patients are shown in Table I. No patient received prior chemotherapy. Palliative radiotherapy to spinal bone was performed in 1 patient and a metastatic tumor of the small intestine was resected in another patient before they received chemotherapy.

Pretreatment levels of serum β-HCG were measured in all 11 patients with poorly differentiated carcinoma. Elevation of serum β-HCG before treatment ranging from 2.0 to 1 023 300 mIU/ml (median 27.6), was observed in 9 of 11 patients with poorly differentiated carcinoma whose tumor histology did not have germ cell features. Pretreatment levels of serum CA 125 were measured in all 20 female patients with adenocarcinoma; elevated levels were observed in 9 patients. All 6 female patients with peritoneal adenocarcinomatosis whose radiological and physical examination did not indicate any lesion of the ovary showed an apparent elevation of CA 125, ranging from 108 to 3980 U/ml (median 631).

Table I. Patient Characteristics (N=50)

| Number of patients (%) |                  |
|------------------------|------------------|
| Age                    |                  |
| median                 | 53               |
| range                  | 27–72            |
| Gender                 |                  |
| male                   | 27 (54)          |
| female                 | 23 (46)          |
| Histology              |                  |
| adenocarcinoma         | 34 (68)          |
| squamous cell carcinoma| 5 (10)           |
| poorly differentiated carcinoma | 11 (22) |
| Performance status by ECOG |          |
| 0/1                    | 38 (76)          |
| 2                      | 7 (14)           |
| 3                      | 5 (10)           |
| Sites of disease       |                  |
| mediastinum            | 10 (20)          |
| retroperitoneum        | 20 (40)          |
| peripheral lymph nodes | 26 (52)          |
| liver                  | 10 (20)          |
| lung                   | 10 (20)          |
| abdominal/pelvic mass  | 9 (18)           |
| pleura/peritoneum      | 16 (32)          |
| bone                   | 15 (30)          |
| others                 | 8 (16)           |
| Number of metastatic sites |            |
| 1                      | 8 (16)           |
| 2                      | 18 (36)          |
| >2                     | 24 (48)          |

Treatment results The treatments of the 50 patients are listed in Table II. Thirty-nine patients received chemotherapy, including cisplatin-based treatment in 23 patients and carboplatin-based in 6. All patients with poorly differentiated carcinoma and all female patients with peritoneal adenocarcinomatosis were treated with platinum-based chemotherapy. Eleven patients did not receive anticancer chemotherapy because of poor performance status in 5 and as a result of the patients’ refusal to consent in 6.

Of the 39 patients who received chemotherapy, 2 patients were not available for evaluation of the response. One female patient with peritoneal adenocarcinomatosis died of treatment-related sepsis 11 days after the first cycle of carboplatin-cyclophosphamide therapy. One male patient with poorly differentiated carcinoma, suffered severe renal and pulmonary toxicities that precluded repeated administration of 5-fluorouracil (5FU)-cisplatin therapy and response evaluation. Both patients were con-
considered treatment failures in calculating the actuarial survival curve.

Among the remaining 37 patients, 4 achieved CR and 9 achieved PR. By intent-to-treat analysis, the overall response rate was 33.3% (95% confidence interval: 19.1–50.2%) and was 35.1% in assessable patients. The responses to treatment are summarized in Table III, according to the clinicopathological categories.

A remarkable response—including 3 CR—was observed in patients with poorly differentiated carcinoma. Among 6 patients with poorly differentiated carcinoma in whom serum β-HCG before chemotherapy was elevated above 10 mIU/ml, 2 CR and 3 PR were achieved (response rate: 83.3%); Table IV details the clinical characteristics of these patients. Of these 6 patients, 4 had tumors located predominantly in a midline distribution, a pattern previously described as indicating platinum sensitivity. It is noteworthy that both of the patients with poorly differentiated carcinoma who were still disease-free at 64 and 34 months, respectively, had extremely elevated serum levels of β-HCG. On the contrary, of the 4 patients with poorly differentiated carcinoma in whom β-HCG was less than 10 mIU/ml, only 1 responded to chemotherapy. Although 2 of these 4 patients had tumors located predominantly in a midline distribution, neither responded to chemotherapy.

A remarkable response was also observed in female patients with peritoneal adenocarcinomatosis treated with platinum-based chemotherapy. Characteristics of these patients are shown in Table V. One complete responder relapsed after an initial CR during 25 months, and is currently alive with disease at 53 months.

In 11 female patients with conditions other than peritoneal adenocarcinomatosis, 7 received platinum-based and 4 received non-platinum-based chemotherapy. In 7 male patients with adenocarcinoma, 4 received platinum-based chemotherapy and 3 participated in clinical trials of new anticancer agents. In these “non-favorable” patients with CUP, chemotherapeutic outcomes were very disappointing.

The median overall survival of all 39 patients treated with chemotherapy was 8 months, with an actuarial 13.9% in 2-year survival. The median overall survival of 11 patients managed with best comfortable care was 4.5 months. The survival curves according to clinicopathological features are shown in Fig. 1. The actuarial survivals at 2 years for patients with poorly differentiated carcinoma in whom β-HCG was more than 10 mIU/ml, for female patients with peritoneal adenocarcinomatosis, and for the remaining patients treated with chemotherapy were 33.3%, 33.3%, and 4.3%, respectively. The survival rate at 2 years in the group of patients with poorly differentiated carcinoma in whom β-HCG was elevated and in female patients with peritoneal adenocarcinomatosis was significantly higher than those in the remaining patients treated with chemotherapy (P=0.011).

DISCUSSION

Despite the development of diagnostic procedures, CUP is not rare in clinical oncology practice. As a result, how patients with CUP should be managed is an important issue. In this retrospective analysis, patients in certain clinicopathological subgroups of CUP were suggested to be sensitive to chemotherapy and might enjoy prolonged survival.

During the last two decades, it has been recognized that well-defined subgroups of patients do respond favorably to
cancer of unknown primary location, specifically with poorly differentiated carcinoma having certain characteristic features, such as age less than 50 years, primary tumor location in the midline, rapid tumor growth, and tumor sensitivity to previously administered radiotherapy or chemotherapy. This clinicopathological entity was called ‘extragonadal germ cell cancer syndrome.’ Similarly, Greco et al. reported on 71 patients with advanced poorly differentiated carcinoma of unknown primary site having at least one of the same clinical characteristics as extragonadal germ cell cancer syndrome. In that study, with intensive cisplatin-based combination chemotherapy, 38 patients (56%) had major responses, including 15 (22%) complete responders, and 9 patients (13%) who remained disease-free for 36 to 67 months. Nevertheless, it was later reported by the same group of investigators that approximately one-third of the patients with poorly differentiated carcinoma of unknown origin who achieved CR were found on re-evaluation of the pathologic material with immunohistochemical techniques to have specific diseases, including lymphomas and germ cell tumors.

**Table IV. Characteristics of Patients with PDC Having β-HCG>10 mIU/ml**

| Age | Gender | Predominant site       | Regimen | Response | Survival (months) | β-HCG (mIU/ml) |
|-----|--------|------------------------|---------|----------|------------------|---------------|
| 52  | male   | midline lymph nodes    | BEP     | CR       | 64+              | 1 023 300     |
| 46  | male   | midline lymph nodes    | BEP     | CR       | 34+              | 35 187        |
| 65  | male   | soft tissues           | BEP     | PR       | 4                | 164           |
| 35  | female | retroperitoneal lymph nodes | CAP | NC       | 8                | 30.7           |
| 27  | female | liver                  | EAP     | PR       | 7                | 27.6           |
| 32  | male   | mediastinal tumor      | BEP     | PR       | 9                | 11.7           |

Abbreviations: B, bleomycin; E, etoposide; P, cisplatin; A, doxorubicin; C, cyclophosphamide; CR, complete response; PR, partial response; NC, no change.

**Table V. Characteristics of Patients with Peritoneal Adenocarcinomatosis**

| Age | Additional sites of disease | Regimen | Response | Survival (months) | CA-125 (U/ml) |
|-----|-----------------------------|---------|----------|------------------|---------------|
| 62  | liver                       | CAP     | CR       | 53+              | 134           |
| 41  | liver                       | CAP     | PR       | 13               | 3980          |
| 60  | —                           | CAP     | PR       | 32               | 1380          |
| 48  | —                           | CBDCA-C | PR      | 13               | 1008          |
| 60  | pelvis, pleura              | CBDCA-C | PD      | 3                | 254           |

Abbreviations: C, cyclophosphamide; A, doxorubicin; P, cisplatin; CBDCA, carboplatin; CR, complete response; PR, partial response; PD, progressive disease.

Fig. 1. Overall survival according to the clinicopathologic categories. — all patients (N=50), —— patients with poorly differentiated carcinoma in whom β-HCG was elevated above 10 mIU/ml (N=6), — female patients with peritoneal adenocarcinomatosis (N=6), —— other patients treated with chemotherapy (N=27), ---- patients with best comfortable care (N=11).
poorly differentiated carcinoma group by immunohistochemistry. After excluding these chemotherapy-sensitive patients, platinum-based chemotherapy still showed an excellent response of 60% in patients with poorly differentiated carcinoma, including 33% CR. Especially, in patients with poorly differentiated carcinoma in whom β-HCG was elevated above 10 mIU/ml, 5 of 6 patients (83%) responded to platinum-based chemotherapy, with 2 complete responders (43%) who have remained disease-free for 34 and 64 months, respectively. These results suggest that extreme elevation of β-HCG might predict chemotherapy-sensitivity.

It remains unclear whether the presence of elevated levels of serum β-HCG might identify patients with better chemotherapy responsiveness and longer survival. Greco et al. reported that elevated levels of β-HCG did not correlate with either response or duration of survival in 66 patients with poorly differentiated carcinoma. Lenz et al. also indicated that elevation of serum β-HCG did not identify the patients having prolonged survival among 74 patients with poorly differentiated carcinoma. Similarly, Currow et al. found that only 2 of 9 patients in whom β-HCG was elevated to more than 8 times the upper normal limit responded to platinum-based chemotherapy. Although the number of patients was small in the present study, significant elevation of β-HCG (>10 mIU/ml; that is, more than 20 times the upper normal limit), might suggest a better response to platinum-based chemotherapy.

Another well-documented subgroup of patients with favorable responses is women with peritoneal adenocarcinomatosis. These patients have been shown to be responsive to chemotherapy, which has proven to be effective in the management of ovarian cancer. For example, Dalrymple et al. reported that a therapy consisting of cisplatin and chlorambucil was effective in 10 of 31 such women, including 3 complete responders and 2 disease-free patients. Similarly, Strnad et al. reported that 7 of 18 women achieved CR with cisplatin-based chemotherapy and 3 of them showed long-term survival. In our study, 4 of 5 women with peritoneal adenocarcinomatosis responded to platinum-based chemotherapy.

Other treatment-responsive subgroups have been described with characteristic clinicopathological presentations, including women with adenocarcinoma involving axillary lymph nodes and patients with squamous cell carcinoma involving cervical lymph nodes. In this study, however, there was no patient belonging to either of these subgroups.

Unfortunately, response rates and survivals in the remaining CUP patients were very disappointing. Several prospective trials have been conducted to improve the outcome of chemotherapy: (1) carboplatin and oral etoposide, (2) docetaxel and platinum, and (3) carboplatin and paclitaxel. The response rates, however, were below 30% and the median survival ranged from 5 to 11 months in these studies. Moreover, the therapeutic outcome did not appear to improve even in high-dose intensive chemotherapy. In this study, half of the patients belonged to the subgroups of male patients with adenocarcinoma and female patients with adenocarcinoma without peritoneal adenocarcinomatosis. The majority of patients with CUP are included in these subgroups. Further investigation of chemotherapy is warranted because of their resistance to existing therapies.

In conclusion, the present study showed that, after appropriate clinical and pathological exclusion, platinum-based chemotherapy provided promising results in patients with poorly differentiated carcinoma and in female patients with peritoneal adenocarcinomatosis. Our data also suggested that, among patients with poorly differentiated carcinoma, significantly elevated serum levels of β-HCG might predict a better response to platinum-based chemotherapy. However, the investigation of novel chemotherapeutic approaches is warranted for male patients with adenocarcinoma and for female patients with adenocarcinoma without peritoneal adenocarcinomatosis.

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