Chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP) is not effective in patients with enteropathy-type intestinal T-cell lymphoma

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Background: Enteropathy-type intestinal T-cell lymphoma (ETCL) is a highly aggressive disease with poor response to conventional CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy. According to promising data with the addition of etoposide (E) to the CHOP regimen (CHOEP) in aggressive lymphomas including T-cell lymphomas, we have treated patients with ETCL with CHOEP chemotherapy.

Patients and methods: Ten consecutive patients (six female, four male) suffering from ETCL were given CHOEP at our institution. Four patients had advanced disease (stage III/IV), while five patients were rated to be in stage II and one in stage I. Treatment consisted of doxorubicin 50 mg/m², cyclophosphamide 750 mg/m² and vincristine 1.4 mg/m² by intravenous infusion on day 1, etoposide 100 mg/m² intravenously days 1–3 and oral prednisone days 1–5. Cycles were repeated every 3 weeks for a maximum of six courses. Assessment of response was done by means of conventional computed tomography scanning, endoscopy and also [18F]fluorodeoxyglucose positron emission tomography (FDG PET) in seven patients.

Results: A total of 41 cycles (median six, range one to six) were administered to our patients. Leukocytopenia/neutropenia WHO grade IV necessitating granulocyte colony-stimulating factor support occurred in all patients evaluable for toxicity, and febrile neutropenia was seen in two patients. Two patients had to undergo emergency surgery due to intestinal perforation after one and three courses of treatment, respectively. Therapeutic results, however, were disappointing: two patients had complete remission (CR), three had partial remissions and five patients progressed during treatment. Remissions, however, where only short-lasting, as only two patients are alive at a median follow-up of 7 months (range 2–16). One patient is in ongoing CR 10 months after initiation of chemotherapy and the other is currently undergoing second-line treatment for progressive disease as judged by follow-up investigations after three cycles of CHOEP.

Conclusions: Our data demonstrate that CHOEP chemotherapy results in a high rate of hematotoxicity in patients with ETCL. In spite of this, therapeutic results were disappointing and do not appear to be superior to conventional CHOP chemotherapy. We conclude that CHOEP cannot be recommended for routine use in patients with ETCL.

Key words: chemotherapy, CHOEP, enteropathy-associated T-cell lymphoma

Introduction

Enteropathy-associated T-cell lymphoma is a rare neoplasm and comprises ~1% of all lymphoma cases and ~5% of gastrointestinal lymphomas [1, 2]. An association between small intestinal lymphoma and villous atrophy of the mucosa not involved by lymphoma was first noted by Isaacson and Wright in 1978 [3]. Owing to the histological characteristics, they assumed that this condition might be a malignancy arising from histiocytes. A later report by Isaacson and coworkers, however, demonstrated monoclonal rearrangement of T-cell receptor b and expression of T-cell-associated antigens consistent with a lymphoma of T-cell origin [4]. In the recent WHO classification of tumors of hematopoeitic and lymphoid tissues, this type of lymphoma is included under the term enteropathy-type T-cell lymphoma (ETCL) [5].

ETCL is an aggressive disease that may either present de novo or arise in the context of long-standing or untreated...
The occurrence of refractory sprue, i.e., clinical and histological worsening of celiac disease (CD) in spite of a gluten-free diet, or the development of ulcerative jejunitis, may herald the progression of CD to overt lymphoma, as monoclonal T-cell populations have been demonstrated in refractory sprue, ulcerative jejunitis and ETCL [6, 7].

According to recent data, patients diagnosed with ETCL face a dismal prognosis [8, 9]. This is largely due to complications arising from peritonitis and malnutrition, and later from progressive disease, typically characterized by intestinal recurrences. Therefore, only ~50% of patients are amenable to chemotherapy and only a small proportion is able to finish the treatment as scheduled; 5-year failure-free survival rates in the range of 3% have been reported [9]. In addition to the poor general condition of patients diagnosed with ETCL, currently applied chemotherapeutic approaches appear to be of limited efficacy in patients with ETCL. The most commonly used therapeutic regimen consists of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Unfortunately, mostly retrospective analyses on the value of chemotherapy in ETCL have been published due to the rare nature of the disease. In the only prospective study available, Daum et al. [8] nevertheless reported a statistically significant survival benefit at 2 years for patients receiving CHOP as compared with untreated individuals. This benefit, however, was restricted to patients in clinical stages I/II (49% versus 14%), while no difference was seen at stages III/IV. Only eight of 23 patients achieved a complete remission (CR) after potential curative therapy, and six of eight patients have relapsed [8].

In view of these sobering data, novel chemotherapeutic approaches are clearly warranted. Recent data have shown promising results with the addition of etoposide (E) to conventional CHOP chemotherapy (CHOEP) in individuals suffering from aggressive lymphomas [10–12]. Among the patients included in these series, efficacy of CHOEP therapy was also demonstrated in individuals diagnosed with T-cell lymphomas of various histologies. Accordingly, we have hypothesized that CHOEP might be an effective regimen in patients suffering from ETCL. In this article, we present our experience with CHOEP in patients with ETCL treated at our institution.

**Patients and methods**

Patients with a diagnosis of ETCL according to the criteria established in the recent WHO lymphoma classification [5] as diagnosed by a reference pathologist (A.C.) were treated with CHOEP chemotherapy. Treatment consisting of cyclophosphamide 750 mg/m², doxorubicin 50 mg/m² and vincristine 1.4 mg/m² (for a maximum single dose of 2 mg) was given intravenously on day 1, etoposide was administered at a dose of 100 mg/m² intravenously days 1–3 along with 100 mg oral prednisone on days 1–5. Antiemetic prophylaxis with 5-HT₃ receptor antagonists was administered on a routine basis before chemotherapy. For initiation of chemotherapy, a left-ventricular ejection fraction >50% as judged by echocardiography, a leukocyte count >3500/µl and a thrombocyte count >100 000/µl, as well as normal liver and renal function parameters, were required. Before initiation of therapy, patients were staged with computed tomography (CT) scan of thorax and abdomen, gastroduodenoscopy, enteroclyisma (CT), colonoscopy and bone marrow biopsy. Seven patients also underwent whole-body positron emission tomography with [18F]fluorodeoxyglucose (FDG PET).

Cycles were repeated every 3 weeks, with re-evaluation of treatment response by means of gastroscopy with biopsies, endosonography and CT scanning of thorax and abdomen every three cycles, and FDG PET as indicated according to our previous experience [13]. Response to treatment was classified according to WHO standard criteria. In case of stable disease (SD), partial remission (PR) or complete remission (CR) of the lymphoma upon re-evaluation, treatment was continued for another three cycles up to a maximum of six cycles. Therapy was discontinued in the presence of progressive disease (PD).

Whole-body FDG PET scans were performed on a GE Advance PET scanner (GE Medical Systems, Waukesha, WI, USA) according to our previously published protocol [13]. FDG PET results were correlated with histological findings of duodenal biopsies and with conventional imaging methods (CT, enteroclyisma CT) and surgical findings, respectively.

**Results**

Ten patients diagnosed with ETCL (six female, four male) aged between 44 and 71 years were given CHOEP chemotherapy between 2000 and 2003 at our institution (for patient characteristics see Table 1). Three patients had a clinical history of CD and had been on gluten-free diet for 20–42 months, respectively. In spite of this, they developed massive diarrhea and weight loss leading to diagnosis of ETCL. Diagnosis was established endoscopically in one of these patients, while biopsies from stomach, duodenum, colon and terminal ileum were initially rated unsuggestive of lymphoma in the other two cases. Owing to worsening symptoms, both underwent surgical exploration for areas rated as potential lymphoma. In one patient, enlarged lymph nodes were seen on both CT and FDG PET, while the latter also suggested lymphoma in the jejunum. In the other case, FDG PET was focally positive in the jejunum, while CT showed diffuse thickening and edema throughout the small bowel.

In total, three of the six patients without a history of CD presented as surgical emergencies due to abdominal perforation, and diagnosis was subsequently established by histological evaluation of the resection specimens. The median WHO performance status was 2 (range 1–3). Owing to an impaired performance status, the first course of therapy was administered at a dose corresponding to 1 m² in one patient (patient 6), and was escalated to full dose for the second cycle.

All patients were judged evaluable for response, while one patient died 6 weeks following application of the first course due to fulminant lymphoma progression before re-assessment of hematological toxicity. Therefore, the patient was considered as PD, and judged not evaluable for toxicity. Another patient had to undergo emergency surgery for multifocal intestinal perforation 10 days following the first course. Following surgery, she developed multiorgan failure due to sepsis and died 8 weeks after the first course. She was also rated as PD, but was considered evaluable for hematoxicity due to serial laboratory investigations performed in the intensive care unit. Side effects were mainly hematological, but were pronounced in all cases. All eight patients evaluable for toxicity developed
pronounced leukocytopenia WHO grade III/IV and granulocytopenia WHO grade IV, necessitating intervention with granulocyte colony-stimulating factor (G-CSF) and prophylactic G-CSF support for the following cycles. Two of these patients developed febrile neutropenia necessitating hospitalization and parenteral antibiotics. Two patients developed anemia WHO grade II rated as treatment-related, and three had thrombocytopenia grade III.

Interestingly, all three patients with a clinical history of CD experienced severe worsening of their pre-existing diarrhea immediately after chemotherapy, necessitating parenteral fluid substitution. Diarrhea, however, subsided after 5 to 8 days, and did not recur during further courses of chemotherapy in spite of maintained doses of all cytotoxic agents.

An objective response was seen in six of 10 patients (three CR, three PR), and all responding patients also had an increase in performance status. In addition, all five of these patients gained >5 kg in weight during the course of treatment. Responses, however, were short in our patients, and only one patient is currently alive after 10 months. Furthermore, after a median follow-up of 7 months, only two patients are still alive, one of them undergoing second-line chemotherapy with fludarabine and cyclophosphamide for PD. Apart from these sobering therapeutic results, the hematotoxicity of CHOEP was high, as all patients developed severe leukocytopenia/granulocytopenia necessitating G-CSF support, and in two patients neutropenic fever leading to hospitalization occurred. These results are in keeping with a German multicenter study, where a high rate of side effects was seen, especially in elderly patients [11].

Of interest is the fact that severe diarrhea accompanied the first course of therapy in all three patients with a clinical

Discussion

ETCL is a relatively rare disease characterized by a dismal prognosis. Only ~50% of patients are able to undergo chemotherapy owing to their impaired performance status due to malnutrition at lymphoma diagnosis, and response rates and survival times are extremely poor [8, 9]. While standard CHOP chemotherapy appears to confer a statistically significant survival benefit to patients with localized disease [8], overall survival is still unsatisfactory. While high-dose chemotherapy with stem cell transplantation has been used in selected patients [9], the majority of patients are not amenable to this form of treatment owing to their highly impaired performance status resulting from chronic malnutrition and cachexia caused by the disease. In addition, novel forms of treatment such as fludarabine-based combinations [14] or the monoclonal CD52 antibody, alemtuzumab [15], are currently being tested in peripheral T-cell lymphomas, but no data on their potential activity in ETCL are available at the moment.

Our data obtained with a more aggressive chemotherapy regimen, i.e. CHOEP, further underscore the frustrating situation in the treatment of patients with ETCL. While objective responses were achieved in six of 10 patients (three CR, three PR), five of these patients have relapsed with only one being in ongoing CR after 10 months. Furthermore, after a median follow-up of 7 months, only two patients are still alive, one of them undergoing second-line chemotherapy with fludarabine and cyclophosphamide for PD. Apart from these sobering therapeutic results, the hematotoxicity of CHOEP was high, as all patients developed severe leukocytopenia/granulocytopenia necessitating G-CSF support, and in two patients neutropenic fever leading to hospitalization occurred. These results are in keeping with a German multicenter study, where a high rate of side effects was seen, especially in elderly patients [11].

Table 1. Characteristics of patients with enteropathy-type intestinal T-cell lymphoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>CD</th>
<th>Perforation</th>
<th>Stage</th>
<th>PS</th>
<th>No. cycles</th>
<th>Response</th>
<th>Status</th>
<th>Survival (months)</th>
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<td>No</td>
<td>Yes</td>
<td>I</td>
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<tr>
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<td>Yes</td>
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<td>1</td>
<td>PD</td>
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</table>

Perforation at presentation (yes/no), after three cycles of treatment and after one cycle.

CD, clinical history of celiac disease; PS, WHO performance status; F, female; M, male; PR, partial remission; CR, complete remission; PD, progressive disease.
history of CD. In all cases, the severity of diarrhea necessitated intermittent parenteral fluid and albumin substitution, but symptoms resolved completely after 5 to 8 days. Patients recovered fully, with consecutive weight gain between 5 and 11 kg in the course of treatment, and diarrhea did not recur for the remaining cycles of chemotherapy.

While ETCL is difficult to assess with conventional non-invasive methods due to the preferential (multifocal) occurrence within the small bowel, our limited results suggest FDG PET as a promising method for diagnosis, staging and follow-up of these patients.

Taken together, our results indicate that more aggressive chemotherapy with the CHOEP regimen results in a high rate of hematotoxicity in patients with ETCL. While objective responses and subjective benefit in terms of weight gain and cessation of diarrhea were seen, this benefit was nevertheless short-lasting and did not translate into apparent prolongation of survival. Thus, CHOEP does not appear to be more active than standard CHOP therapy in this cohort of patients, and cannot be recommended for routine use.

References