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Original Article

Toxicities, safeties and clinical response of dacarbazine-based chemotherapy on neuroendocrine tumors in Taiwan population

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Abstract

Background: Currently, the role of dacarbazine (DTIC) based chemotherapy in neuroendocrine tumors (NETs) in Asia is unclear. Here, we report the outcomes of dacarbazine (DTIC)-based chemotherapy in Taiwan population.
Methods: DTIC alone (250 mg/m^2/day), or 5-fluorouracil (5-FU, 500 mg/m^2/day) and DTIC (200 mg/m^2/day) with or without epirubicin (200 mg/m^2/day), for 3 days, every 3−4 weeks. Subgroups were analyzed by grading, and by Ki-67 index.
Results: 48 patients were reviewed in this study, including 3 had grade 1 tumors, 23 had grade 2, while 22 were grade 3. In grade 3 NEC patients, the tumor Ki-67 index of 21−55% were noted in 8 patients, and >55% in 14 patients. Progression-free survival (PFS) was 5.1 months, and overall survival (OS) was 31.6 months. The PFS (in months) were 12.5 and 1.8 for patients with NETs and neuroendocrine carcinomas (NECs), respectively ($p < 0.001$). The OS were not reached and 5.9 months for patients with NETs and NECs, respectively ($p = 0.001$). Patients with NECs were divided into two groups, according to their Ki-67 index. In patients with a tumor Ki-67 index of 21−55%, PFS was 4.1 months, and OS was not reached; in those with a tumor Ki-67 index of >55%, they were 1.5 and 1.8 months, respectively ($p < 0.001$ and $p = 0.013$).
Conclusion: NETs, and grade 3 NECs, with Ki-67 indices of 20−55% had good responses to DTIC-based chemotherapy, with acceptable side effects. Ki-67 index could predict prognosis for grade 3 NEC patients, and guide further chemotherapy choices.

Keywords: Dacarbazine; Ki-67 index; Neuroendocrine carcinoma; Neuroendocrine tumors; Overall survival; Progression-free survival

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Neuroendocrine tumors (NETs) are rare neoplasms characterized by heterogeneous behavior, and have the ability to secrete a variety of hormones, resulting in various clinical syndromes.[1] Although NETs are rare diseases, their incidence has steadily increased over five times in the past 30 years.[2] The prognosis of NETs is heterogeneous. Therefore, World Health Organization (WHO) classified gastroenteropancreatic neuroendocrine tumors (GEP-NETs) into NET grade 1 (G1), NET grade 2 (G2), and neuroendocrine carcinoma (NEC) grade 3 (G3) based on their Ki-67 proliferation index.[3] Surgical resection is the only potentially curative therapy.[4] However, most patients are diagnosed with advanced stage disease.[2,3] Therapeutic options for metastatic G1 and G2 GEP-NET treatment include hormone therapy with a somatostatin analog; targeted therapy; interferon-α therapy; and transcatheter arterial chemoembolization and radiofrequency ablation for local regional control.[4,5] Chemotherapy may be more appropriate as early-line therapy in patients with bulky, or symptomatic, or rapidly progressive tumors, particularly of pancreatic origin.[6] Standard frontline treatment for metastatic G3 NEC uses a combination of etoposide and cisplatin (EP), for which the median duration of response is about 8−9 months.[7−9] An alternative chemotherapy regimen—a combination of streptozotocin, 5-fluorouracil (5-FU), and doxorubicin—was proposed for treating G1 and G2 NETs. However, due to the renal toxicity of streptozotocin, temozolomide, or dacarbazine (DTIC), was substituted in some countries, and the response rates were 16−30% in the previous study.[7,10−12]

Grade 3 NECs are a heterogeneous group, and not considered a single disease entity. Sorbye et al. demonstrated that NECs could be further classified using a Ki-67 index cutoff of 55%.[13] Patients with a tumor Ki-67 index of <55% had a lower response rate to cisplatin-based chemotherapy, but they survived longer compared to patients with a tumor Ki-67 index of ≥55%.[13] NEC patients with tumor Ki-67 indices of 21−55% had better prognoses, irrespective of platinum-based chemotherapy treatment. This finding may lead to the selection of another chemotherapy regimen, rather than EP, for patients with a tumor Ki-67 index of <55%. Some case studies have suggested that DTIC-based chemotherapy could be the second-line treatment, after frontline treatment with etoposide and cisplatin.[13,14] However, no study has investigated use of this regimen in Asia, as either frontline or second-line treatment. In this study, we retrospectively evaluated tumor response, progression-free survival, and overall survival for NET patients who received DTIC-based chemotherapy.

2. Methods

2.1. Study population

This study has been approved by the Ethics Committee of Taipei Veterans General Hospital and Chang Gung Memorial Hospital. Clinical data, including, age; gender; Tumor-Node-Metastasis staging information; tumor site; performance status; functioning symptoms; and, side effects of chemotherapy were obtained through a detailed retrospective review of the medical records of 48 patients with NETs, who had received DTIC-based chemotherapy between January 2010 and January 2016.

In all cases, histological diagnosis was confirmed by two pathologists, and classification of NETs was based on the WHO classification.[3]

Grade of histological differentiation, immunohistochemistry, and Ki-67 staining index were assessed.

2.2. Treatment and evaluation

2.2.1. Regimen

The chemotherapy regimen consisted of the intravenous administration of dacarbazine (220 mg/m^2/day) alone for 3 days, every 3 weeks; 5-FU (500 mg/m^2/day) and dacarbazine (200 mg/m^2/day) with (FDE) or without (FD) epirubicin (200 mg/m^2/day) for 3 days, every 3−4 weeks. If feasible, and in the absence of disease progression after 3 cycles, at least 6 cycles were scheduled. Antiemetics were administered at each course of therapy. Granulocyte colony-stimulating factor was used as secondary prophylaxis in most patients, and as primary prophylaxis in frail patients.

2.2.2. Response, survival, and toxicity evaluation

Computed tomography scan was used for tumor restaging every 3 months, or performed to document disease progression based on clinical symptom deteriorated, and response was assessed using RECIST 1.1. After discontinuation of treatment, patients with no clinical progression symptoms were followed up every 3 months, until disease progression or death. Disease control rate was defined as complete response, partial response, or stable disease. Overall survival (OS) was defined as the time from receiving DTIC based chemotherapy until the date of death due to any cause, or, until the date when lost to follow-up. Progression-free survival (PFS) was defined as the time from receiving DTIC based chemotherapy until the date of documented disease progression, relapse, or death due to any cause; or the date when lost to follow-up after DTIC-based therapy. Toxicity was evaluated and recorded, according to version 4.0 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute.

2.3. Statistics

Categorical variables were expressed as percentages, and continuous variables were presented as median (range, minimum to maximum). The χ^2 test or Fisher's exact test was used to assess qualitative variables. Results were considered significant if P values were <0.05. The distributions of PFS and OS were estimated by Kaplan−Meier curve and log-rank test analyses. Kaplan−Meier curve analyses were performed for PFS and OS, using SigmaPlot version 12.5 (Systat Software, Inc.).

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