Pemetrexed-induced Eyelid Edema: Incidence and Clinical Manifestations

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Abstract. Background: Pemetrexed-induced eyelid edema is a rare side-effect of pemetrexed treatment. Patients and Methods: Retrospective analysis of the incidence and severity of eyelid edema was conducted in patients treated with pemetrexed in a single institution. Results: Eighty-six patients received pemetrexed-containing chemotherapy either as a single agent (45 patients) or in combination with cis- or carboplatin (41 patients). Two patients (2.3%) with stage IV non-small cell lung cancer (NSCLC) presented the edema typically localized in the lower eyelid after first-line treatment with carboplatin-pemetrexed. The edema remained identical in both patients during treatment and regressed in one patient in whom treatment was withdrawn. No other localizations of edema were observed in these patients. Conclusion: Pemetrexed-induced eyelid edema may be more frequent than originally reported. The physiopathological mechanism and, as a consequence, the treatment and/or prevention of this apparently benign side-effect remains unknown.

The novel multiple targeted antifolate pemetrexed has recently been introduced in clinical practice for the treatment of mesothelioma and non-small cell lung cancer (NSCLC) as a single agent or in combination with platinum agents in first or further lines of therapy (1-3). To avoid severe pemetrexed-related toxicities such as hematological and/or dermatological adverse events, premedication with folinic acid, vitamin B12 and corticosteroids has been recommended (3). Edema of the eyelid is considered a very rare side-effect of pemetrexed use and according to an update of the Pemetrexed Clinical Investigator’s Brochure, May 2008 version (Eli Lilly Belgium personal communication) this side-effect was reported in 6 patients out of 1364 treated in monotherapy (0.4%). The present report details the incidence of eyelid edema and the patient characteristics in a single institution.

Patients and Methods

Only patients without eyelid edema at the onset of pemetrexed-containing chemotherapy were included in the present retrospective analysis. The patients were treated with pemetrexed as a single agent or in combination with platinum agents (cis or carboplatin) from June 2003 until May 2010 inclusive. Three-weekly cycles of pemetrexed (500 mg/m²) as a single agent or in combination with cisplatin (75 mg/m²) or carboplatin (area under the time concentration curve, AUC 6) were administered intravenously (i.v.) through an implanted central venous catheter. Standard premedication consisted of an intramuscular injection of 1000 µg of vitamin B12 one week before the onset of chemotherapy and of continuous orally administered folinic acid 0.4 mg per day. In addition, 4 mg of oral dexamethasone was taken in the morning and the evening the day before, the day of and the day after chemotherapy. Antiemetic treatment with alizapride (100 mg i.v.) in patients with single agent pemetrexed and with oral aprepitant (120 mg, 80 mg and 80 mg on days 1 through 3), i.v. tropisetron (5 mg on day 1) and oral methylprednisolone (32 mg on days 1 through 3) in patients with combination treatment was applied.

Screening for subjective and laboratory toxicity was performed before each chemotherapy administration or at any time at the request of the patient. In cases of an unexpected adverse event (like the eyelid edema reported here), complementary examinations (CT of the chest, echocardiography, determination of serum and urine protein levels and thyroid function) were performed.

Results

Eighty-six patients received a pemetrexed-containing regimen during the observational period, either as a single agent (45 patients) or in combination with cis- or carboplatin (41 patients). The characteristics of the patients are detailed in Table I. Most of the patients had advanced non-small cell lung cancer (NSCLC) or mesothelioma. In the first-line treatment, the vast majority received pemetrexed in combination with cis- or carboplatin (19 and 20 respectively). Six patients with first-line combination treatment continued with pemetrexed as a single agent as...
maintenance treatment until progressive disease. Two patients who achieved an objective response after initial induction treatment, but who eventually relapsed were retreated with the same pemetrexed combination at relapse. The total number of all the cycles of pemetrexed administered was 392.

The vast majority of the patients were treated from 2007 onwards when the drug became commercially available. From 2003 until 2007, the drug was used mainly in the frame of three studies: two patients with breast cancer (single agent), three patients with SCLC (combination with carboplatin) and fifteen with mesothelioma (platin-combinations). The two patients who developed the eyelid edema had NSCLC and were treated in 2010. Before that, no such adverse event was noticed. In both the patients, the edema developed abruptly during first-line treatment, approximatively 8 and 10 days after the 3rd and 4th cycle of carboplatin-pemetrexed in a 70-year-old male and a 55-year-old female, respectively. The edema could best be described as a ‘pocket’ containing fluid, with a thin glossy skin covering the pocket at the level of the lower eyelid (Figure 1). Although specific guidelines for scoring of the severity of eyelid edema were not available in the current recommendations for reporting adverse events, the Common Terminology Criteria for Adverse Events v. 3.0 system (CTCAE) (4), a score of grade 2 (visible moderate edema without functional impairment) was attributed to both patients. No concomitant edema or fluid retention was observed in other body parts. In both patients, the necessary examinations to rule out cardiac failure, a nephrotic syndrome, thyroid dysfunction or a deep venous thrombosis of the superior cava vein or central catheter were performed and considered negative. A tentative diagnosis of a chemotherapy-related adverse event was made. The side-effect was considered as subjectively unpleasant by the patients, but was not life-threatening nor did it have a serious impact on the quality of life. Treatment with pemetrexed as a single agent was continued in one patient while in the other pemetrexed was omitted and carboplatin was continued as a single agent. In the latter patient, the edema partially regressed to a grade 1 on further follow-up. The chemotherapy was not modified because of the occurrence of the edema. No specific local or systemic treatment was initiated.

**Discussion**

Edema of the eyelid is a rare adverse event of pemetrexed use. To date, only two patients have been published as case reports in the literature (5, 6) and one additional abstract has been presented recently (7). According to the most recently updated Pemetrexed Investigator’s Clinical Brochure (May 23, 2008), six cases out of 1364 patients treated with single
agent pemetrexed have been reported in clinical trials to have developed eyelid edema (0.4%) (Eli Lilly Belgium, personal communication). According to the published data, the two patients suffering from this adverse event were treated with single agent pemetrexed as a second-line and developed the side-effect after the first (5) and second (6) cycle of pemetrexed. Both patients had been treated before with cisplatin-gemcitabine (5) or carboplatin-paclitaxel (6). The onset of the eyelid edema without manifestation of fluid retention in other parts of the body was sudden and unexpected after 8 and 10 days of treatment. Both patients were not exposed to over hydration nor suffered from cardiac failure, the nephrotic syndrome, hypoproteinemia and/or thyroid dysfunction. The occurrence of two patients with eyelid swelling treated in our institution corroborated well with the previous findings. Some differences in the treatment characteristics are however obvious: in both of the present patients, carboplatin-pemetrexed combination was administered as a first-line therapy. In one patient, initially three cycles of cisplatin-pemetrexed were administered followed by one cycle of carboplatin-pemetrexed (cisplatin was replaced by for carboplatin because of digestive intolerance to the former) but potential residual cisplatin-related toxicity e.g. fluid retention due to hyperhydration was absent. In one Japanese patient (5), no prophylactic steroids were given with pemetrexed administration, while they were in the other reported patient (6) and in our two patients. No risk factor(s) for the eyelid swelling could be extracted from the clinical characteristics of the present and the published patients, nor from the Lilly database.

The pathogenesis of the eyelid swelling remains unknown. The swelling has been suggested to follow the same path as that produced by docetaxel (8). This drug causes capillary protein leakage resulting in oedema in the soft tissues and non-malignant effusions (8). Prophylactic administration of corticosteroid during administration of docetaxel delays and decreases the severity of this side-effect (9). Against this hypothesis, docetaxel-induced edema is not limited to the eyelid while pemetrexed-induced edema is limited to the eyelids. However, in eight recently reported patients with generalized fluid retention while receiving pemetrexed-containing chemotherapy, the eyelid edema was observed in four (7 ).

Other agents such as the tyrosine kinase inhibitors imatinib and nilotinib also can be accompanied by eyelid swelling (10, 11). This side-effect is ascribed to the platelet-derived growth factor receptor-inhibiting activity of these drugs leading to an increase in the interstitial fluid pressure of the eyelid and eventually to edema. The antifolate methotrexate, in use for many years, has not been reported to induce eyelid edema. In summary, the eyelid edema observed in our patients was probably due to the pemetrexed, although it cannot be excluded that a standard concomitant medication or the excipients for pemetrexed formulation could have been the causative agent. In this regard, it is interesting to note that we only observed this toxicity recently. According to the manufacturer of the drug the excipients used were not recently changed (Eli Lilly Belgium, personal communication). Pemetrexed treatment induced edema of the eyelid at a rate of 2.3% of the patients treated. This side-effect is apparently benign and does not lead to treatment modification. The pathogenesis is unknown and there is no specific treatment. With a potentially increasing use of this drug in more tumor types and with more extended use (e.g. maintenance treatment in NSCLC) (12) it is probable that its incidence may increase. Basic and clinical research should continue in order to understand the underlying pathogenesis of this eyelid swelling better so as to define patients at risk and to prevent and treat this not severe but highly ‘unpleasant’ side-effect.

Inclusion of the specific symptoms of this adverse event in the CTCAE reporting system may help in objectivating its severity and allow comparison of similar cases in the scientific literature.

References


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