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Combination of Cytotoxic Therapy for Metastatic Breast Cancer Resulting in Paralytic Ileus

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We report a 40 year old Bahraini female, a case of metastatic breast cancer who experienced paralytic ileus, an uncommon acute complication of Navelbine therapy when it was given in combination with Docetaxel. The diagnosis was made on clinical examination and confirmed by a plain X-ray of the abdomen, which showed multiple fluid levels. The management was conservative in view of the acute toxicity of Navelbine therapy being self-limiting.

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Navelbine (Vinorelbine) a product of Pierre Fabre Oncological laboratories-France is a new cytotoxic drug. It is cytostatic and belongs to the vinca alkaloid group. The molecular target of its activity is tubulin microtubule dynamic equilibrium[1]. Its indications have recently been extended for non-small cell lung cancer and metastatic breast cancer. A multicenter study of single agent Navelbine as first line therapy in advanced breast cancer, which included 157 patients, has confirmed the initial experience in a phase II trial using weekly Navelbine, giving an overall response rate of 41%[2]. This response rates has been confirmed by other trials[3, 4]. Phase I and phase II trials have been conducted to study the recommended dose and the dose limiting toxicity was found to be myelosuppression[5, 6]. The gastrointestinal complications are constipation, nausea and vomiting, but the incidence of these complications is relatively low. Digestive autonomic nervous system toxicity is manifested as paresis leading to constipation (28%) and paralytic ileus is reported to be very rare[1].

As the multiple combination chemotherapy regimens are used extensively in oncological care the side effects, which are uncommon and rare, are occasionally encountered in routine clinical practice. This case report adds further data on rare toxicities to chemotherapy.

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THE CASE

A premenopausal Bahraini lady aged 40 years P2 G2, presented with a lump in her left breast of two months duration in April 1998. A fine needle aspiration biopsy carried out at a private hospital in Bahrain confirmed the diagnosis of infiltrating ductal carcinoma.

She underwent wide excision and axillary dissection in Germany in May 1998, the pathological stage being $T_1N_0M_0$. The Oncologist in Germany advised local radiation therapy followed by a regular follow up. The radiation therapy was administered to the whole breast with boost dose to the primary tumor site at Salmaniya Medical Complex, Bahrain. The cosmesis of breast was excellent but during her regular follow-up, she presented with shortness of breath in August 1999. A metastatic work up was done which included clinical examination, complete blood picture, liver function tests, tumor markers, chest x-ray, bone scan and ultrasound liver. The investigation showed pleural effusion with pulmonary secondaries with no evidence of recurrence in the left breast.

She was prescribed palliative combination chemotherapy in the form of FAC regime (5Flurouracil 600mg/M^2,Adriamycin 60mg/M^2 and Cyclophosphamide 600mg/M^2) once in three weeks for six courses.

This was concluded in December 1999 with partial response assessed by chest x-ray, CT scan, tumor markers and reduction in her symptoms. She was continued with hormonal therapy in the form of tamoxifen. The response, however, was of short duration, and there was progression in her disease status documented by CT scan in February 2000.

The options of further management were discussed with the patient and the family members. Second line chemotherapy was advised with Navelbine and Taxotere (Navelbine 20 mg/M^2 Day 1 and Day 5,Taxotere 85mg/M^2 Day1, once in three weeks) The first course was tolerated well with only grade-1 nausea and vomiting. A day after the second course the patient complained of abdominal pain and constipation. It was not associated with nausea or vomiting. On clinical examination there was minimal abdominal distension and bowel sounds were sluggish. The abdominal distension increased and by the fourth day clinical examination suggested silent abdomen. An X ray abdomen revealed multiple air- fluid levels and distended bowel loops (Fig. 1 & 2). She was managed conservatively and by the 7th day the abdominal distension reduced after the bowels opened normally. A repeat abdominal X-ray on the 10^{th} day was normal.

Figure 1. Erect X-ray of the abdomen. Multiple air fluid levels (black arrows) are seen in the small bowel loops suggestive of acute intestinal obstruction. Incidentally noted pleural effusion on the left side.

Figure 2. Supine X-ray of the abdomen. Multiple distended small bowel loops noted.

The combination chemotherapy was complicated by grade 4 neutropenia with fever, which was managed with antibiotics.

DISCUSSION

Women with metastatic breast cancer are essentially non responsive with standard therapy and hence efforts have been made to give treatment with maximum tumor suppression and to minimize the toxicities. The current approach to adjuvant therapy results in an increasing number of patients who receive an anthracycline based regimen with the cumulative cardiac toxicity as the limiting factor[7]. The need has therefore emerged for nonanthracyclin containing regimen for patients with relapse. Navelbine as single agent in metastatic breast cancer in phase II studies showed response rates of 40%[2,3]. Hence multiple studies of combination chemotherapy with Navelbine have been reported[1,8]. The limiting toxicities of navelbine – taxotere combination therapy is myelosuppression, mainly neutropenia (77%) which was encountered in our case. Sensory neurotoxicity was reported to be about 57% (mild to moderate) and 13% experienced hyporeflexia[8].

Autonomic neurotoxicity manifested as constipation with 7% grade two and 2% grade three. The other gastrointestinal toxicities of nausea, vomiting, mucositis and diarrhoea were generally mild and uncommon[1].

About twenty abstracts from 34th annual meeting of American Society of Clinical Oncology, 1998 and 89th annual meeting of American Association of Cancer Research, 1998 involving Navelbine with other agents was reviewed. The dose limiting toxicity on review of the world literature was neutropenia (70%), and gastrointestinal manifestations of nausea/vomiting and constipation mild to moderate. The digestive autonomic nervous system toxicity leading to paralytic ileus was not observed in the literature reviewed[9].

In a study conducted by L Romero et al[8] of thirty patients who underwent combination chemotherapy with Navelbine and Taxotere as first line for metastatic cancer one patient developed paralytic ileus. Similar toxicity was reported in one patient by Marc Spilmann et al in a study of ninety seven patients with metastatic cancer who received Navelbine

and Doxorubicin[1]. The case presented had paralytic ileus which has been managed conservatively suggesting the self limiting nature of Navelbine toxicity[1,8].

CONCLUSION

The uncommon acute toxicity of paralytic ileus due to Navelbine therapy is the first to be encountered at our Oncology center. Reporting of this case adds to the data already published and will be useful to Oncologists as the use of Navelbine in non small cell lung cancer and metastatic breast cancer is ever increasing. This toxicity could be exaggerated when Navelbine is given in combination with Docetaxel, which is known to have gastrointestinal toxicities.

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