Efficacy of dexamethasone in the management of malignant small bowel obstruction in advanced epithelial ovarian cancer

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Abstract
Introduction Malignant small bowel obstruction (MSBO) occurs in up to 50% of women with advanced epithelial ovarian cancer (EOC) causing symptom burden and distress to women and their families, particularly in the terminal stages of the disease. Corticosteroids are used to promote symptom resolution in malignant small bowel obstruction (MSBO) related to EOC, with little published data on their efficacy, optimal dosing and duration of treatment.

Objective To evaluate the efficacy of dexamethasone in achieving symptom control in women with advanced EOC presenting with MSBO, assess dexamethasone dosing and efficacy over subsequent presentations, and examine differences in dexamethasone responsiveness between platinum-resistant and platinum-sensitive patient.

Methods This is a retrospective cohort study of women presenting with MSBO due to advanced EOC over a 12-year period from January 2005 to December 2016 in a single tertiary hospital.

Results Ninety-one women with MSBO were administered dexamethasone over 154 admissions with 89% of women initially achieving partial or complete symptom control. Dexamethasone responsiveness did not change with recurrent admissions, and platinum responsive patients were more likely to respond to dexamethasone than platinum-resistant patients (OR 3.6 [95%CI 1.1 to 12.2, p = 0.04]). A total of 15.6% of patients required additional measures to control symptoms of MSBO, and 44.8% had adequate symptom resolution to allow them to remain on or commence further treatment for EOC.

Conclusion Dexamethasone therapy is a useful adjunctive therapy in the management of symptoms associated with MSBO in women with EOC.

Keywords Intestinal obstruction · Carcinoma · Ovarian epithelial · Dexamethasone · Palliative care

Introduction

Ovarian cancer was the 17th leading cause of death for females in Australia in 2019 with 1081 deaths reported [1]. In metastatic ovarian cancer, malignant bowel obstruction (MBO) has an estimated incidence of 20–51% [2–6]. Median survival following MBO has been reported as 13–19 weeks [3, 5–7]. MBO is reported in up to 77% of women with advanced ovarian cancer [7]. Bowel obstruction in ovarian cancers more commonly involves the small bowel (61% vs large bowel 33%) with both sites involved in greater than 20% of patients [8, 9]. Malignant small bowel obstruction (MSBO) in advanced ovarian cancer is thought to be due to several factors: diffuse intra-peritoneal carcinomatosis infiltrating the bowel wall with oedema and accumulation of intramural cytokines leading to dysfunctional bowel motility; large volume deposits causing extrinsic or intramural occlusion from tumour...
growth; mesenteric and coeliac plexus deposits affecting the autonomic nerve supply and adhesions preventing normal peristaltic action [10, 11]. Symptoms include colicky abdominal pain, anorexia, progressive nausea, vomiting, reflux, abdominal distention and cessation of flatus. Prolonged MSBO is complicated by malnutrition, dehydration and electrolyte abnormalities. MSBOs are distressing to women and their families and commonly require prolonged and recurrent inpatient hospital admissions during the terminal phase of their illness. Furthermore, acute MSBO can preclude the commencement of subsequent lines of cytotoxic therapies in eligible patients meaning MSBO needs to be managed to facilitate further therapy where indicated.

Historically, MSBO was treated with either nasogastric tube, intravenous fluid and electrolyte therapy or palliative surgery, often with inadequate management of the patient’s symptoms. In 1985, a study of 38 patients in whom surgery was not a viable option suggested that management with corticosteroids shortened hospital length of stay and decreased the duration and severity of patient symptoms [12].

Despite the common occurrence of MSBO in relapsed ovarian cancer, there is an absence of level 1 evidence or national guidelines to aid management. Furthermore, there is no clear definition of “successful management” in MSBO. Despite attempts to establish clear criteria for randomised trials for malignant bowel obstruction, noting the importance of an observational arm and composite QOL outcome measures [13], a paucity of prospective, randomised trials means that most evidence comes from small case series, retrospective reviews and cohort studies, and management relies on clinicians’ personal experience and individualisation of care.

A Cochrane review published in 2000 on the use of corticosteroids for the resolution of MBO in advanced gynaecological and gastrointestinal cancer identified very limited data but suggested a potential benefit, with a trend towards faster resolution of bowel obstruction using corticosteroids. Although limited by data quality, the morbidity from corticosteroid use appeared to be very low. It should be noted that the Cochrane review used a heterogeneous population with different histological subtypes and no distinction regarding the site of obstruction [14].

Corticosteroid actions are multifactorial and not completely understood. Corticosteroids are thought to provide anti-emetic and co-analgesic effects and to reduce peri-tumour and peri-neural inflammatory oedema, improving intestinal motility. There is uncertainty about their efficacy, the optimal choice of steroid, route of administration, dosing regime and duration of treatment [14]. Short-term side effects from steroid administration include delirium, sleep disturbance, proximal muscle weakness, gastric ulceration, infection risk and worsening of glycaemic control in diabetic patients.

We present a retrospective cohort study of the use of one specific corticosteroid (dexamethasone) for MSBO at our centre. This study aims to further inform evidence regarding the effectiveness of dexamethasone for MSBO in advanced EOC. It also aims to inform evidence regarding the duration and dose of corticosteroid and response.

**Materials and methods**

This is a retrospective cohort study conducted at the Mercy Hospital for Women, a tertiary women’s hospital in Heidelberg, Victoria, Australia, caring for approximately 55 women per year with newly diagnosed with ovarian cancer. The study included all women treated with dexamethasone who had a history of epithelial ovarian cancer (all histopathological subtypes and stages) with advanced disease and were admitted with a MSBO or combined small and large bowel obstruction between 1 January 2005 and 1 December 2016.

The primary outcome was to evaluate the efficacy of dexamethasone in achieving full or partial symptom control in patients with advanced epithelial ovarian cancer presenting with MSBO. The secondary outcomes were (1) to evaluate whether the efficacy of dexamethasone declines during subsequent admissions with recurrent MSBO; (2) to compare dexamethasone dosage required to achieve symptom control in the first versus recurrent episodes of MSBO and (3) to compare the efficacy of dexamethasone in chemotherapy refractory, platinum resistant and platinum sensitive disease.

Data was obtained from review of the patient medical record. The diagnosis of bowel obstruction was based upon a patient’s signs, symptoms and imaging during admission (abdominal X-ray or computerized tomography (CT) of the abdomen pelvis). A diagnosis of partial bowel obstruction was made when there was ongoing passage of flatus and liquid stool, whereas complete bowel obstruction was diagnosed in the setting of failure to pass flatus and liquid stool and/or an empty rectum on radiography. The medical record was reviewed to determine patient demographics including age, 2014 International Federation of Gynaecology and Obstetrics (FIGO) stage at diagnosis, histopathological subtype, site of primary disease, date of diagnosis, date of death; primary treatment; recurrence data; number of presentations with MSBO; MSBO symptoms, dexamethasone dosage and duration; alternate management (including surgery); resolution of MSBO with symptom control and clinical outcome.

Complete symptom control was defined as discharge (to home or other, including palliative care facility) on full diet with resolution of all symptoms. Partial symptom control was defined as symptom improvement as reported by the patient and discharge tolerating clear or free fluids and oral...
medication with possible mild persistent symptoms such as nausea and or vomiting.

Conservative management of MSBO included nil by mouth (ice for comfort), intravenous fluids, electrolyte optimisation, analgesics, antiemetics and anti-reflux medication (usually a proton pump inhibitor). Other interventions in selected cases only included the use of a nasogastric tube (NGT), gastrograffin enema, percutaneous endoscopic gastrostomy (PEG) tube, ascitic tap or surgery. Usual dose of dexamethasone was 8 mg/day with a reducing dose of 4 mg/day following resolution of symptoms.

Platinum-resistant disease was defined as evidence of progressive disease (radiological, clinical or biochemical) within 6 months of completing first line platinum-based chemotherapy.

Women who had evidence of isolated large bowel obstruction (where surgery is more often required) and women who had no evidence of advanced ovarian cancer as a cause of their obstruction were excluded, as were women with MSBO occurring during primary therapy (either perioperatively or during first-line chemotherapy). Analysis was truncated for the first six admissions with MSBO.

Patient characteristics and outcome data were summarized as mean (SD), median [25th to 75th percentile] and number (%) according to type and distribution. For outcomes, the precision of percentage point estimates was presented as 95% confidence intervals calculated using the Wilson score test. Assessment of longitudinal change across presentations for responsiveness and dosage per was performed using a marginal mean model using generalized estimation equations with robust standard errors and an exchangeable correlation structure. All statistical tests were two-sided, with a *p* value of <0.05 considered significant. Statistical analysis was performed using Stata v16 statistical software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, T. USA).

Ethics approval was obtained through the Mercy Health Human Research Ethics Committee (Reference number R16/50, approved 11 October 2016).

**Results**

One-hundred and fifty-four admissions for 91 patients met inclusion criteria (Fig. 1). Baseline characteristics are displayed in Table 1. A total of 76.9% of patients were diagnosed with FIGO stage 3 disease and 16.5% with FIGO stage 4 disease. The median interval from cancer diagnosis to the first presentation with MSBO was 22.9 months [IQR 11.1–46 months]. The median interval from diagnosis of cancer recurrence to MSBO was 10.9 months (IQR 2.8–25.0 months). The median number of admissions with MSBO was one [IQR 1–2]; however, 25% of women had three or more admissions for MSBO.

The presenting symptoms are described in Table 2. Ninety-three per cent of all presentations were due to partial small bowel obstruction and 7% to complete small bowel obstruction (Table 3).

**Primary outcome**

The details of dexamethasone responsiveness and dosing are presented in Table 4. Overall, 137 (89%) admissions were associated with a complete or partial response to dexamethasone.

**Secondary outcomes**

Based upon the longitudinal regression model, there was no statistically significant difference in mean responsiveness over repeated admissions (*p* =0.14), and the predicted mean responsiveness for any admission was 89% (95% CI 84 to 94).

The median duration of dexamethasone dosing was 4 to 6 days, and the median daily dose was between 6 and 8 mg, predominantly prescribed in a twice daily dosing schedule. The median total dose was between 26 and 40 mg. Doses were not statistically different across admissions (*p* =0.96) with predicted mean daily dose of 6.5 mg (95%CI 6.0 to 7.0).

Platinum-sensitive patients were more likely to respond to dexamethasone compared to platinum-resistant patients (OR 3.6 [95%CI 1.1 to 12.2, *p* =0.04]) (Table 4). In addition, there was no statistical difference in dexamethasone responsiveness between first and subsequent presentations for either platinum-sensitive or -resistant patients (*p* =0.11).

The median length of stay ranged from 5 to 7 days and was not statistically different between presentations.

Across all admissions, additional treatments were used to aid in resolution of symptoms in 16% of cases, notably 6% needed an ascitic tap, 6% needed NGT placement and 3% required an exploratory laparotomy, adhesiolysis and bowel resection/bypass procedure and/or loop ileostomy.

Regarding management after presentation with MSBO, 38% of women received end-of-life care, 6% were observed but 45% remained on disease treatment (continued or commenced chemotherapy, clinical trial, hormonal therapy or radiotherapy). The median time from first presentation with MSBO to death was 3.8 months (IQR 1.9–9.8).

**Discussion**

**Key findings**

This retrospective cohort study demonstrates a complete or partial response rate of 89% in patients administered...
dexamethasone when presenting with MSBO. There was no difference in response to treatment over multiple presentations with MSBO. In addition, we have shown that platinum-sensitive patients are more likely to have symptom control than platinum-resistant patients after treatment for MSBO. Patients required additional therapies to resolve their MSBO relatively infrequently. Median duration of therapy was 4 to 6 days and median daily dose 6 to 8 mg. This study confirms that short-term mortality is high following first presentation with a MSBO associated with recurrent disease with a median survival of 3.8 months.

**Comparison to previous studies**

Our retrospective review is one of the largest datasets of women with advanced EOC and MSBO to examine the efficacy of dexamethasone. Complete or partial resolution of symptoms after receiving dexamethasone for treatment of MSBO is higher in our study that previously reported. In a study of 35 patients with MBO treated with dexamethasone versus placebo, Hardy et al. found resolution rates of 37% vs 22% respectively [15]. A prospective study by Philip et al. of 13 patients found 69% response to a 3-day minimum course of dexamethasone [16]. Laval et al. studied 52 patients treated with methylprednisolone versus placebo and showed a non-statistically significant trend towards higher symptom resolution (59% versus 33.5%) [17]. The low resolution of symptoms in these studies may be because treatment success or failure was assigned on day four of treatment in the study by Laval et al. [16], as well as the use of methylprednisolone rather than dexamethasone and the smaller patient numbers in both studies. The inclusion of bowel obstruction at all levels (gastric outlet, small and large bowel) may also account for differences in results.

Use of other therapies in our study is lower than that reported in other studies. Tran et al. found that amongst 49 patients with MBO, 42.9% required surgery and 14.3% required other interventions, such as stent placement [4].
A Surveillance, Epidemiology, and End Results registry (SEER) database review of 1397 women who were admitted with bowel obstruction more than 6 months post stage II–IV ovarian cancer diagnosis showed that 40% underwent surgery, and 11% had a gastrostomy or jejunostomy tube placed [18]. Explanations for this could be that the SEER database review did not limit patients to those with malignant bowel obstruction secondary to advanced disease and so surgical intervention for other indications such as incarcerated hernias and adhesions would have been included.

Our study confirms numerous previous findings of poor median survival after presentation with MSBO [3, 5–7]. Tran et al. described a cohort of 311 patients with recurrent ovarian cancer, of which 49 had bowel obstruction after recurrence. Of these, 29 lived less than 6 months after their bowel obstruction [4].

**Implications of our study findings**

Our study population is representative of the Australian population due to a broad referral base. Our results support the use of dexamethasone in the supportive treatment of MSBO in advanced EOC. The results can be used to counsel women who present with a MSBO in the context of advanced EOC. Importantly, given our study supports previous data that shows median survival is short, priority should be given to helping women develop an advanced care plan in consultation with their support people and treating practitioners. Despite poor long-term survival, over 40% of women remained on or re-commenced treatment. As this is a retrospective review, it is unclear the extent to which counselling, acknowledgment of treatment goals and shared decision making went into such treatment decisions for these women.

The goals of management of women with MSBO in the setting of advanced EOC should be regarded as palliative and, in general, avoidance of surgery is advisable. Interventions that do not facilitate further chemotherapy do not appear to be associated with an improved survival and should be considered palliative [8, 18, 19].
Future directions

An interprofessional MBO program incorporating non-surgical management (including pharmacological therapy) and prioritising an outpatient model of care would provide an organised framework to coordinate the complex care needs of a patient between multiple disciplines and so optimise her experience. A pilot program was introduced in a large Canadian cancer centre and resulted in a statistically significantly shorter length of stay in hospital (13 vs 22 days) and an improved median overall survival (99 vs 243 days) adjusted for stage and lines of chemotherapy [2]. Important components included patient educational material for patient empowerment, specialised oncology nurses leading telephone consultations in between clinic appointments, multidisciplinary team review of the cases and treatment consensus based on standardized clinical assessment tools and finally, electronic documentation to facilitate timely in and outpatient care. Education of the patient, her family and community medical carers about MSBO and possible early intervention, offers the potential to improve quality of life and is worthy of further evaluation. It is possible that incorporating the early use of corticosteroids for MSBO, in carefully supervised outpatient setting, for patients being palliated for advanced ovarian cancer, may further improve such programs.

Strengths and limitations

This study is one of the larger datasets of women with advanced EOC and MSBO to be published; however, its limitations stem from the fact it is a retrospective, single centre observational review. No data on possible adverse effects from corticosteroid administration or the patient’s experience from taking corticosteroids could be collected, but the morbidity from steroid administration appears to be low in this setting [20]. An acknowledged limitation is the use of symptom resolution as documented by the clinicians’ entries in the patient’s medical records; whilst clinicians may underreport their patient’s symptoms, the objective documentation of oral intake (either solids or liquids) was reliably recorded in the patient’s medical record. Patients who did not receive dexamethasone for an admission were not included in analysis, limiting the ability to perform a comparative review of effectiveness of dexamethasone versus no dexamethasone. Given dexamethasone is standard of care in this unit, those who did not receive this treatment were selected because they had mild or resolving symptoms, and therefore, due to this selection bias, no comparison was performed. In addition, malignant small bowel obstruction in advanced ovarian cancer is a condition which may have a natural history of relapsing and remitting. Some women did not commence dexamethasone within 24 h of their admission, so their MSBO symptom resolution may reflect the natural disease process rather than benefit from steroids.

Conclusion

Dexamethasone therapy achieved 89% complete or partial symptom control in women who have advanced EOC presenting with MSBO, whose life expectancy is under 4 months after first presentation. Duration of therapy was 4 to 6 days with a 6- to 8-mg median daily dose. Quality of life is critical in any palliative intent treatment, and patient preferences should be evaluated in future studies assessing patient-centred outcomes and patient-reported experience measures from the management of their bowel obstruction, including steroid use and its possible side effects and their place in the management of a bowel obstruction. Adequate control of symptoms should be defined by the patient group and national guidelines. Incorporating multidisciplinary MBO care will likely improve patient experience at the end of their lives.

Author contribution All the authors contributed to the study conception and design. Data collection performed by AJ, MM and NJ. Analysis was performed by RH. The first draft of the manuscript was written by AJ, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.
Data Availability Data was obtained from the patients’ medical record.

Code availability Statistical analysis was performed using Stata v16 statistical software (StataCorp. 2019. Stata Statistical Software: Release 16, College Station, T. USA).

Declarations

Ethics approval Ethics approval was obtained from the Mercy Health Human Research Ethics Committee. (Reference number R16/50, approved 11 October 2016).

Consent to participate As retrospective data was obtained from the medical record, the need to obtain consent to participate was waived by the Mercy Health HREC.

Consent for publication N/A

Competing interests The authors declare no competing interests.

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