

RESEARCH ARTICLE

Can Megestrol Acetate Induce Thrombosis in Advanced Oncology Patients Receiving Chemotherapy?

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Abstract

Background: Megestrol acetate (MA) is a steroid origin medicine often used for control of cachexia in oncologic palliative care. Thrombosis is a common problem in oncology patients. One question is whether MA can cause thrombosis. This retrospective, registry-based analysis was therefore conducted to assess thrombotic processes in oncology patients using MA concurrent with chemotherapy. **Materials and Methods:** Data on oncology patients at the metastatic stage using MA were obtained from the archives of our center. Outcomes of patients were evaluated for thromboembolic events (VTEs) during treatment. **Results:** Ninety-seven oncology patients with a median age of 62 (33-84) years were included. During the median follow-up of 17 months, 58 (59.8%) died leaving 39 (31.2%) still alive. Median overall survival (OS) was 19 months (6-180). Mean time of MA use was 8.69 months (± 3.53), with a median dose of 160mg (range 160-480mg). Eleven VTEs were detected after MA use, 4 of these in pancreatic cancer cases. The patients with thrombosis non-significantly had worse OS, than those without thrombosis ($p=0.106$). **Conclusions:** This trial revealed that the 11.3% of all patients developed thrombosis, who had been treated with MA and chemotherapy concomitantly. There was no statistically significant difference regarding to occurrence of thrombotic process, among the patients receiving different chemotherapy regimens with MA concomitantly. Pancreatic cancer seemed to be related to thrombosis rather than MA use.

Keywords: Megestrol acetate - oncology - thrombosis - palliative care - cancer cachexia

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Introduction

Normal appetite involves peripheric and central pathways. The neuropeptide-Y (NPY) neurons in the arcuate nucleus of the hypothalamus have strong orexigenic effect by combined interaction of hepatic glucose, insulin, and adipocyte released leptin in peripheric pathway. NPY neurons with proopiomelanocortin also play critical role with interaction of leptin and serotonin in central pathway (Topkan et al., 2007).

Cancer induced cachexia (CIC) occurs as a result of decreased caloric intake (possibly due to causes such as gastrointestinal tumors or chemotherapy-induced nausea and vomiting), an increased metabolic state, or the production of proinflammatory mediators such as interleukin-1-2-6, tumor necrosis factor- α and interferon gamma. CIC is experienced by up to 80% of patients with advanced stage cancers, particularly those with gastrointestinal, pancreatic, thoracic and head and neck malignancies (Norleena et al., 2012).

Megestrol acetate (MA), is a synthetic derivative of progesterone, and the most widely used drug in CIC (Morley et al., 2006; Megace, 2012). The precise mechanism of action of MA is unknown but research in

murine models suggests that its effect may be partially mediated by NPY, a potent centrally acting appetite stimulant (Norleena et al., 2012). A number of human studies and meta-analysis show that various doses of MA stimulate appetite and increase weight gain (Desport et al., 2000; Berenstein and Ortiz, 2005; Zhan et al., 2013). The US Federal Drug Administration approved megestrol acetate for the treatment of anorexia, cachexia or cancer at the 1993. Loprinzi et al. suggested that a 160mg daily dose of MA is optimal for appetite stimulation (Loprinzi et al., 1993).

Venous thromboembolism (VTE) includes the development of either deep vein thrombosis or pulmonary embolism. VTE can occur in a substantial number of patients with cancer even without clinical symptoms. The risk factors for VTE are a previous VTE or a family history of VTE, restricted mobility, age more than 40 years, cancer, infection, obesity, varicose veins, and smoking. VTE is a major cause of morbidity and mortality in patients with advanced solid tumors (Sorensen et al., 2000; Chew et al., 2006; Khorana et al., 2010). It's well known that VTE increases in patients with cancer (Aleem et al., 2012).

The average annual incidence of VTE in the general

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population is about 0.1% (Heit, 2008). Patients with cancer are at a 4 to 7 times greater risk of VTE than patients without cancer, mainly due to thrombogenic processes related to the disease and treatment (Heit et al., 2000; Blom et al., 2005; Blom et al., 2006). While receiving chemotherapy, cancer patients have a 7-fold risk of developing VTE as compared with other patients without cancer (Mandala et al., 2011). In addition, some medications may increase the risk of VTE. One study of nursing home residents identified a high incidence of VTE in those treated with MA (Bolen et al., 2000). Patients with cancer who use MA potentially share many of the same thrombogenic mechanisms, including increased levels of clotting factors as well as decreased levels of anticoagulant proteins. Even if there is a study that MA did not increase thrombogenic potential in cancer patients (Oberhoff et al., 2001), a lot of studies had also pointed out the risk of thrombosis related to MA in patients with cancer (Ruiz et al., 2013).

Many randomized trials have determined the safety, efficacy, and ideal dose of MA when used for appetite stimulation. The optimal dosing and possible thrombogenic effects of MA remain uncertain. Despite of the risk for VTE in patients with cancer is well known, the risk in patients who use MA with chemotherapy concomitantly is less clear. So, we aimed to examine the association between MA treatment and venous thrombotic process in a variety of metastatic malignities treated with chemotherapy.

Materials and Methods

Patients with various metastatic cancers who were treated with MA concomitant with chemotherapy were included in the study. Patients were excluded from the study who had ECOG PS worse than 2, age smaller than 18 years old, who had experienced any thrombotic process and used heparin for prophylactic treatment.

Between January 2013 and June 2014, a total of 97 patients with metastatic cancers were found to be suitable for the study from the files of the cancer patients in central archive of the hospital.

Statistical Analysis

SPSS version 17 for windows was used for the statistical analysis. Survival differences were calculated

using the Kaplan-Meier method. Description of the populations used in the study was based on percentages and their 95% confidence intervals (95% CI) for categorical data, and median and extreme values for continuous data. The chi-squared test was used to investigate the association between variables and thrombosis related categoric outcomes. $p \leq 0.05$ value is considered to be statistically significant.

Results

All patients provided informed consent for their information to be stored in the hospital database and be used for research. We identified 97 consecutive patients diagnosed with a variety type of metastatic cancer and had been prescribed MA for palliative treatment. Median follow-up time and median age were 17 months (range, 6-65 months), and 62 years (range, 33-84 years), respectively. Most of the patients were diagnosed with lung cancer of 25.7%, pancreatic cancer of 17.5%, colorectal cancer, of 13.4%, gastric cancer of 13.4%, breast and gynecologic cancer of 12.3%, in order. During the follow-up, there were 58 (59.8%) deaths. Fifty (51.5%) patients had 2 ECOG performance and 47 patients (48.5%) had 0-1 ECOG PS. Thirty six patients (37.1%) were women.

All of the patients had been given concurrent chemotherapy with MA for palliative treatment. The median MA treatment duration was 7 months (range 4-19). Among 97 patients there were 11 (11.3%) patients with venous thrombosis after MA treatment. We haven't found statistically significant correlation between MA using and thrombotic events in terms of both chemotherapy regimens (e.g. cisplatin, taxanes, fluorouracil and targeted therapy vs others) and chemotherapy schedule (combination or single chemotherapy). Five of the eleven patients had received platin based chemotherapy. There was no statistical difference between the patients who have thrombosis and the patients who have not thrombosis in terms of OS. However, there was increased trend for OS of the patients who have not thrombosis ($p=0.106$).

Among 11 patients majority were metastatic pancreatic disease (4 of 11 patients were pancreatic cancers Table 1). Despite metastatic pancreatic cancer patients tend to develop thrombosis after MA uses, we didn't find any significant relationship between thrombotic process and type of diagnose (e.g. lung, gastric, gynecologic and breast

Table 1. The Patients with Metastatic Disease who Experienced Thrombosis Receiving MA with Chemotherapy Concomitantly

patient	age	gender	PS	diagnose	Situ-ation	chemotherapy	Follow-up (months)	MA duration (months)	rt	Weight increase
RY	76	W	2	uterine	ex	Paclitaxel-carboplatin	15	6	+	-7
IC	75	M	2	lung	ex	Docetaxel-cisplatin	10	5	+	+1.5
GD	65	M	2	pancreas	ex	gemcitabine	17	5	-	+2.2
AS	55	W	2	pancreas	ex	gemcitabine	23	8	-	+4.2
RE	68	M	2	pancreas	ex	Cisplatin-gemcitabine	18	10	-	-1.2
HAC	61	M	1	pancreas	live	Cisplatin-gemcitabine	6	5	-	+2
UA	74	W	1	breast	live	Epirubicin-cyclophosphamide	60	13	+	+8
MS	76	M	2	colon	live	Folfiri-bevacisumab	10	5	+	-6
KA	59	M	1	colon	ex	Folfiri-erbitux	18	6	0	+10
NG	69	M		gastric	Ex	5-fluorouracil-folinat	19	6	+	+4.5
MS	48	M	2	gastric	ex	DCF	20	5	+	+5

*DCF(docetaxel-cisplatin-5-fluorouracil), M (man), W (Woman), PS (Eastern Cooperative Oncology Group Performance status), rt (radiotherapy), MA (megestrol acetate)

Table 2. Relationship with the Factors and Thrombosis Occurrence

	Thrombosis (+)	X ² =Asymp. Sig. (2-sided)
cisplatinvs others (+/-)	4/36vs 7/61	0.956
5-FUvs others (+/-)	4/37vs 7/60	0.897
Targeted Txvs others (+/-)	2/14	9 / 8 3 0.719
Taxanesvs others (+/-)	3/30vs 8/67	0.781
Combinationvs single (+/-) (chemotherapy)	8/77vs 3/20	0.562
Radiotherapy (+/-)	5/47vs 6/50	0.776
Exitus (+/-)	8/58vs 3/39	0.630
Age > 60vs ≤ 60 years	8/55vs 3/42	0.255
Weight increase (+/-)	9/59vs 2/38	0.130
Lung Cavs others (+/-)	1/25vs 10/72	0.179
Pancreas Cavs others (+/-)	4/17vs 7/80	0.081
MA Duration ≤7vs >7 months	8/51vs 3/46	0.155
MA Dose ≤160vs >160mg	5/45vs 6/52	0.947
ECOG PS ≤1vs > 1	3/47vs 8/50	0.135
BSA <1.79vs ≥1.79	5/45vs 6/52	0.947

cancers). There was no significant difference regarding to development of thrombosis, for MA dose, treatment duration, gender and radiotherapy in metastatic cancer patients who were used MA for palliation. Table 2.

Discussion

CIC is thought to be a very late and irreversible condition in natural history of cancer and its management is considered as an integral part of palliative care in terminal stage cancers. The metabolic, biochemical, and molecular changes showed that most of the factors can be present at the time of diagnosis even in the absence of weight loss (Topkan et al., 2007). Therefore, loss of appetite and cachexia should be managed from the beginning of disease till end of life in cancer patients.

The true incidence of VTE in cancer patients is not known due to the presence of a number of different confounding factors (Seddighzadeh et al., 2007). Variable rate of VTE in different studies is likely to be due to multiple factors which include variation in types of cancer and presence of various treatment modalities.

Addition of MA for appetite and cachexia in cancer patients who have already had hypercoagulable state of malignancy may increase the incidence of thromboembolic phenomena. It has been known that cancer patients receiving chemotherapy are at enhanced risk of VTE as compared to patients not receiving chemotherapy (Otten et al., 2004; Khorana et al., 2007). VTE is the most common vascular complication of antineoplastic therapy. Almost half of patients may have additional risk factors for thrombosis (Aleem et al., 2012). The interrelationship between cancer and thrombotic process is well illustrated. Increased morbidity resulting from hospitalization and anticoagulation use, bleeding complications, reduction in quality of life increased the risk of recurrent VTE and cancer treatment delays are significant clinical and economic consequences due to cancer and treatment related VTE (Chen et al., 2014). A venous thrombotic event may impact the chemotherapy routine and potential therapeutic approaches. Moreover, the hemostatic system itself could contribute to tumor cell survival, disease

progression, and metastatic cancer (Kuderer et al., 2009). Thus, all patients with cancer should be assessed for VTE risk on admission.

While some antineoplastic agents cause thrombotic process, there is limited data about risk of thrombosis if metastatic cancer patients is treated with MA concurrently with chemotherapy for appetite stimulation. Antineoplastic chemotherapy induces VTE, in addition to increased thrombogenesis in malignancy. In a study, symptomatic VTE occurred in 1.9 percent over a median follow-up 2.4 months or a rate of 0.8 percent/month after one cycle chemotherapy (Khorana et al., 2005). The impact of chemotherapy initiation on the incidence of VTE was demonstrated in a retrospective study of 17284 ambulatory patients with advanced cancer who were initiating systemic chemotherapy (Khorana et al., 2013). Compared with age-matched controls, patients with advanced cancer had a nine-fold increased risk of VTE within the first year of initiating chemotherapy (12.6 percent versus 1.4 percent).

It has not been clearly determined whether megestrol acetate increases the incidence of thromboembolic phenomena in cancer patients. In a previous placebo-controlled trial of 133 patients, only one thromboembolic episode was noted and this was in a patient who was receiving the placebo (Loprinzi et al., 1990). Other trials involving cancer anorexia/cachexia patients have noted a less than 5% incidence of thromboembolic phenomena in both MA and placebo groups (Bruera et al., 1990; Tchekmedyian et al., 1991). In our study, higher rate of patients (11.3%) had VTE events who received MA concomitantly with chemotherapy when compared to literature. We considered that MA has more thrombogenic effect when it is combined with chemotherapy. In another study, the patients with advanced small cell lung cancer who received MA concomitant with chemotherapy (cisplatin-etoposide) had 9% incidence of thromboembolism with megestrol acetate versus 2% with placebo. The result was statistically significant (p=0.01) (Seng et al., 2012).

Most common chemotherapeutic agents associated with VTE are L-asparaginase, thalidomid analog and cisplatin. Despite of 5 of 11 patients to whom developed thrombosis had been received cisplatin-based chemotherapy, we didn't found any difference on rate of VTE occurrence, in terms of type of chemotherapy regimen with addition of MA. Besides, the cancer patients who received MA with combination chemotherapy had similar rate of VTE occurrence when we compared the patients treated with single agent. Later study revealed that, there was a trend for more thromboembolic events in patients randomized to higher MA doses (>800mg). Similar trends were reported in the two dose-response trials involving women with breast cancer (Cruz et al., 1990; Abrams et al., 1992). This subject is necessary to be determine whether megestrol acetate, especially at higher doses, has risky for VTE. There was insufficient information to define the optimal dose of megestrol acetate although therapeutic doses typically ranged from 100mg to 1600mg per day, with efficacy shown between 400-800mg daily (Tchekmedyian NS and Hickman M. 1992). In some other literature,

consideration of using a lower megestrol dose (eg, 160 to 480mg/d) could be eligible based on positive results previously reported by some investigators using these lower doses (Bruera et al., 1990; 1996).

Parnes and colleagues performed a randomized dose-finding study for MA in 382 cancer patients with cachexia, receiving MA doses of 125mg, 625mg, or 1,250mg corresponding to low-, medium-, and high-dose groups, respectively. VTE occurred in 9 patients with no differences between the three groups (Parnes et al., 1999). The results of another study suggest that higher doses of MA were more effective for weight gain than lower doses. But, incidence of VTE in patients taking high-dose (>400mg) MA was nearly three times higher than that of patients taking low-dose (<100mg) (Brandon and Russel, 2012).

In a meta-analysis performed by Maltoni and colleagues; eleven of the 15 studies and showed that patients on a high-dose progestin treatment were more than twice as likely to gain weight as were those patients on placebo, whereas most studies reported mild side-effects were not statistically different in the treated arm with respect to the control arm in cancer patients with anorexia cachexia (Maltoni et al., 2001).

In our study median MA dose was 160mg (range 160-480mg). We didn't observe any relationship between doses of MA used concomitantly with chemotherapy with regard to occurrence of VTE.

Localisations of cancer with the highest rates of VTE included pancreas, kidney, ovary, lung, and stomach. In our study, sites of cancer with the VTE were pancreas, colon, stomach and other, respectively. Table 1. According to a validated model pancreatic cancer is one of very high risk factor of cancer diagnosis (Khorana et al., 2012). Despite being non-significant majority of cancer diagnosis associated with VTE, was metastatic pancreatic cancer in our study. However, in a study pancreatic cancer had been classified "other" group, because of the relatively low incidence rates (Chen et al., 2014). For this reason, the relationship of cancer diagnosis and VTE should be further studied in larger sample sizes.

This study was limited in that its retrospective nature did not permit conclusions to be attributed to direct causes and effects. Because of heterogeneity and limited number of patients, it could not be enough for differentiation between the thrombogenic effects of MA and those of cancer and its treatments, the very high rate of VTE in these patients suggests that treatment with MA may be contributory.

In conclusion, the high rate of VTE in these patients suggests that concomitant chemotherapy with MA may be contributory factor. MA that was used concomitantly with chemotherapy does not seem to generate significant difference rate of VTE, regarding either chemotherapy regimen or types of cancers. While MA seems to be effective for appetite stimulation, a thorough risk assessment for VTE should be performed in patients with cancer prior to initiating treatment with MA especially patient with pancreatic cancer should be followed-up for risk of thrombosis.

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