Review Article

ผลของยาโอลันซาปีนต่อการเพิ่มน้ำหนักตัวในผู้ป่วยมะเร็งที่มีภาวะผอมหนังหุ้มกระดูก

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บทคัดย่อ

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ว. เภสัชศาสตร์อีสาน 2555; 8(3) : 1-9
Received : 27 July 2011 **Accepted :** 30 November 2012

ผู้ป่วยมะเร็งจำนวนมากได้รับความทุกข์ทรมานจากภาวะไม่อยากอาหาร ภาวะอิ่มเร็ว และการรับรู้รสผิดปกติ อันเป็นผลจากโรคมะเร็งที่ก่อให้เกิดภาวะเบื่ออาหาร (cancer-related anorexia) การประเมินภาวะผอมหนังหุ้มกระดูก (cachexia) จะพิจารณาจากอาการทางคลินิก อันได้แก่ น้ำหนักลด (ควรวินิจฉัยแยกโรคจากภาวะของเหลวคั่ง) และผลกระทบต่อคุณภาพชีวิต (Quality of life: QOL) ของผู้ป่วย พยาธิสรีรวิทยาการเกิดภาวะผอมหนังหุ้มกระดูก มีความสัมพันธ์กับระดับฮอร์โมนแอแนบอลิกที่ลดลงร่วมกับความผิดปกติในกระบวนการเมแทบอลิซึมโปรตีน ไขมันและคาร์โบไฮเดรต ยาโอลันซาปีนเป็นยารักษาโรคจิตเวชหลายชนิด โดยออกฤทธิ์ยับยั้งการทำงานของตัวรับซีโรโทนีน (Serotonine: 5-HT_2, 5-HT_3) โดปามีน (Dopamine: D_2) และ ฮีสตามีน (Histamine: H_1) ซึ่งมีผลในการรักษาภาวะผอมหนังหุ้มกระดูกได้ รายงานการเกิดอาการไม่พึงประสงค์จากการใช้ยาโอลันซาปีนพบว่ามีระดับรุนแรงน้อย ได้แก่ ง่วงซึม, น้ำหนักเพิ่ม และ ผลกระตุ้น metabolic effects

คำสำคัญ: ผู้ป่วยมะเร็งที่มีภาวะผอมหนังหุ้มกระดูก, ผู้ป่วยมะเร็งที่มีภาวะเบื่ออาหาร, น้ำหนักลด, สภาวะทางโภชนาการ, โอลันซาปีน, คอร์ติโคสเตอรอยด์

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Olanzapine induced weight gain in patients with cancer-related cachexia

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IJPS, 2012; 8(3) : 1-9

Abstract

Most cancer patients suffer from loss of appetite, early satiety, and taste changes, which are the systemic effect of cancer and lead to cancer-related anorexia. Cancer cachexia is characterized by the clinical presentations of weight loss (corrected for fluid retention) and lower quality of life (QOL). The pathophysiology of cachexia involves the decrease of anabolic hormones and an alteration of protein, lipid, and carbohydrate metabolism. Olanzapine (OLN), an antipsychotic agent which blocks the 5-HT_2, 5-HT_3, D_2 and H_1 neurotransmitter receptor is used to treat several psychotic diseases with some reported side effects: sedation, weight gain, and positive metabolic effects.

Keywords: cancer-related cachexia, cancer-related anorexia, weight loss, nutritional status, olanzapine, corticosteroids

Introduction

Cachexia is a persistent and harmful complication of advanced cancer. The sequence of anorexia, unintentional weight loss, tissue loss, poor performance status, decreases quality of life (QOL) and eventually leads to death (Inui, 2002; Mantovani and Madeddu, 2010). About half of cancer patients experience anorexia in their course of disease and the treatment with chemotherapy may exacerbate anorexia by causing dysphagia, nausea, vomiting and mucositis (Navari and Marie, 2012). Cachexia usually occurs either in the young age or elderly and becomes more severe as the disease progresses (Inui, 2002).

Many cancer patients suffer from pain, depres sion, constipation, malabsorption, and the side effects of treatment such as nausea and vomiting from chemotherapy. These lead to a decrease of food intake and cause anorexia and eventually cachexia.

The pathogenesis of cancer-related cachexia remains unclear. There are several hypotheses to explain the mechanism. The comprehensible explanation is leptin hormone which plays role in regulating fat storage. Tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-γ (IFN- γ), produced by the tumor or by the host response to the tumor, also affect the food intake and energy expenditure both directly and indirectly (Figure 1) (Tisdale, 1997; Inui, 1999; Moldawer and Copeland, 1997; Plata-Salaman, 2000).

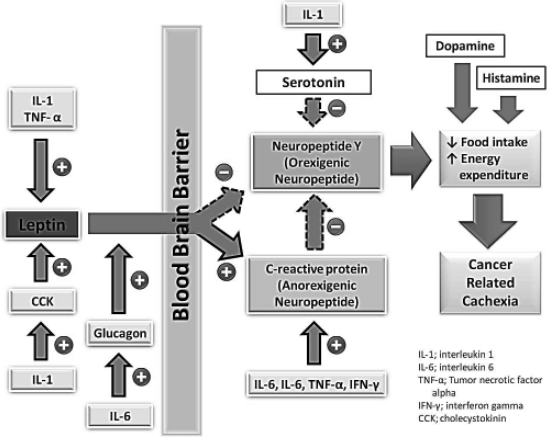

Figure 1 Factors involved in pathogenesis of cancer-related cachexia (Adapted from Inui, 2002)

Measuring patient's nutritional status to detect cachexia includes clinical assessment combined with

anthropometric tests such as skin fold thickness, and mid-arm circumference. However, the easiest and most commonly used method in a clinical setting is body weight. By monitoring weight changes during the course of cancer treatment, physicians can predict and determine the severity of cancer-related cachexia (Burman and Chamberlain, 1996).

Treating primary cancer results in a decrease in cachexia. Since most advanced cancer diseases could not be cured and an enteral nutrition is difficult for many patients, other novel strategies are needed to be studied to incorporate in their treatment. Several drugs have been used to treat cachexia but the results are not quite satisfactory. Many clinical trials could not demonstrate a significant difference in improving weight gain or quality of life (Boddaert *et al.*, 2006).

Effective treatments of cancer-related cachexia

1. Progestagens, such as medroxyprogesterone acetate (MPA) and megestrol acetate (MA), are considered the best choices for treatment of cancer-related cachexia nowadays, and they also have been approved in Europe for treatment of cancer and AIDS related cachexia. However, the efficacy of progestagens is not very impressive. The improvement of short-term appetite stimulation was less than 30% in patients treated with MA (Loprinzi *et al.*, 1990). And although weight gain was achieved, it did not show a better quality of life or longer survival (Loprinzi *et al.*, 1999; Jatoi *et al.*, 2002). Progestagens cause weight gain by accumulation of fluid and fat but not increased lean body mass (LBM), which is the main target in the treatment of cancer-related cachexia. Nevertheless, it was approved by US FDA for the treatment of AIDS-related cachexia and currently it is the most widely studied agent for cancer-related cachexia (Table 1) (Mantovani and Madeddu, 2010).

2. Corticosteroids have been evaluated in many randomized controlled trials. Evidence has shown that they can increase appetite and improved quality of life in cancer-related cachexia (Moertel *et al.*, 1974; Willox *et al.*, 1984). MA and corticosteroids appeared to be equally effective, but in long-term use, there are more side effects including myopathy, diabetes, water and salt retention, and adrenal suppression and crisis (Loprinzi *et al.*, 1999). Therefore, corticosteroids are not a good choice for chronic use and should be applied only in the pre-terminal phase of cachexia.

Table 1 Currently available therapeutic approaches and emerging drugs for the treatment of cancer-related cachexia (Mantovani and Madeddu, 2010)

	Level of evidence[a]
Drugs commonly used	
Progestagens: megestrol acetate/ Medroxyprogesterone acetate	1
Corticosteroids	1
Drugs with a strong rationale that failed or did not show univocal results in clinical trials	
Omega-3 fatty acids-EPA	1
Cannabinoid (dronabinol)	1
Bortezomib	3
Emerging drugs with some effective results but still under clinical evaluation	
Thalidomide	2
Ghrelin	2
COX-2 inhibitors	2
Insulin	2
Branch chain amino acid	n.a.
Oxandrolone	2

[a] 1:randomized controlled trial, systematic review, 2: prospective cohort study, 3: case-control study, retrospective cohort study

n.a.: not applicable

Olanzapine: Drug review

Olanzapine is an atypical antipsychotic agent belonging to thiobenzodiazepine class. It was approved in 1996 by United State Food and Drug Administration

(US FDA) for the treatment of schizophrenia in adults and adolescents and is currently the only treatment for both acute phase and maintenance of mixed or manic episodes associated with bipolar I disorder (McDonagh *et al.*, 2010).

Olanzapine binds to numerous neurotrans mitter receptors, including the histamine 1 (H_1) receptors with highest affinity, serotoninergic 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, and 5-HT_6 receptors with high affinity and dopaminergic D_1, D_2, D_3, D_4, D_5, and muscarinic M_1-M_5 receptors with medium affinity. It also binds to adrenergic α_1 and α_2 receptors, γ-amino butyrate $(GABA)_{a1}$ receptor, and the benzodiazepine binding sites with low affinity (Bymaster *et al.*, 1996). Olanzapine regulates diverse signaling pathways within the brain and the extracellular signal-related kinase in chronic use (Ann and Linmarie, 2010; Fumagalli *et al.*, 2006). Nowaday, the mechanism of olanzapine induced weight gain is unclear. Nevertheless olanzapine may produce weight gain via blockade of several neurotransmitters receptor such as 5-HT_{2c}, 5-HT_3, D_2 and H_1 receptor. The serotoninergic system particularly is important in food and body weight regulation (Lam *et al.*, 2010).

Olanzapine has good bioavailability with good absorption by oral administration and reaches maximum concentrations in 5 hours in adults with a half-life of 21-54 hours. Sixty-five percent of drugs are excreted by kidneys in urine while the rest in feces within 7 days (Callaghan *et al.*, 1999). It is metabolized via the liver mainly by glucuronidation, allylic hydroxylation, oxidation, and dealkylation. Oxidation occurs primarily within the cytochrome P450 enzyme (CYP1A2) (Kando *et al.*, 1997; Callaghan *et al.*, 1999). Factors that affect drug levels are smoking (reduce 30% of plasma level), gender (increased plasma level 85% in female) (Callaghan *et al.*, 1999), drug interaction with carbamazepine (decreased plasma level), fluvoxamine and other selective serotonin reuptake inhibitors (SSRIs) (increased plasma level). The elimination half-life ranges from approximately 27 hours in smoker to 37 hours in nonsmoker and in general the pharmacokinetics was similar between adolescents and adults (Theisen *et al.*, 2006).

The normal dose of olanzapine in schizophrenia is 10-20 mg per day; in agitation, dementia, and delirium, the doses range from 2.5 to 20 mg single dose or divided doses twice a day (Natalia *et al.*, 2002). A main side effect is weight gain, particularly in children and adolescents. Extrapyramidal symptoms (EPS), including akathisia, tardive dyskinesia, seizure, and neuroleptic malignant syndrome can be observed in patients treated with high dose regimen. Compared to typical antipsychotics, olanzapine has fewer events of EPS, drug interactions and neutropenia (Ann and Linmarie, 2010).

The US FDA approved olanzapine for the treatment of schizophrenia or manic/mixed states in bipolar disorder but it was not approved to treat dementia or dementia-related psychosis, and caution should be used before using olanzapine in elderly people with dementia because of increases risk of death (black box warning). However, the side effects particularly weight gain and lipid dysregulation are prominent and may cause overweight and diabetes mellitus (Natalia *et al.*, 2002). Healthcare providers should discuss these points with the patient and family when starting the treatment.

Clinical study of olanzapine: safety, efficacy and weight gain effects

Olanzapine was compared with conventional antipsychotic haloperidol, focusing on weight change and metabolic factors (non-fasting serum glucose, serum cholesterol, and diastolic blood pressure). The study included 1996 patients randomly assigned 2:1 to olanzapine, 5 to 20 mg/day, or haloperidol, 5 to 20 mg/day. The mean weight gain in olanzapine-treated patients was 6.26 kg. This was significantly higher than that of haloperidol group, which was 0.69 kg ($p < 0.001$). Patients with higher BMI (> 27.6) gained less

weight during treatment with olanzapine than their lighter counterparts ($p < 0.001$). The effect of olanzapine dose on weight was not significant ($p \geq 0.183$). Median serum glucose at endpoint was not significantly associated ($p = 0.096$) with weight change. There was no difference in serum glucose, cholesterol, and diastolic blood pressure between the olanzapine and haloperidol groups ($p > 0.05$) (Bruce *et al.*, 2001). Another study compared olanzapine with haloperidol in the treatment of schizophrenia, schizoaffective and schizophreniform disorders. Olanzapine was shown to be more effective on all six measurements. The difference of weight gain between olanzapine and haloperidol treatment were significant ($p<0.001$), the mean weight gain being 1.88 kg and 0.02 kg, respectively. However, a post hoc analysis revealed that low body mass index (BMI) was significantly more likely to have gained weight during treatment with olanzapine (Tollefson *et al.*, 1997). A randomized double-blinded study for a 12-week period was demonstrated the effects of clozapine, olanzapine, and haloperidol on weight and metabolic parameters such as plasma glucose, cholesterol, and triglyceride level. One hundred and ten patients with schizophrenia or schizoaffective disorder were randomized for the trial, but only 93 patients had both baseline blood level and a subsequent blood level. Thirty-four, 31 and 28 patients received clozapine, olanzapine and haloperidol respectively. There was a statistically significant difference among three groups in weight gain and rising of plasma glucose and lipid level. Olanzapine-treated patients gained the most weight, while clozapine-treated patients had an increase level of cholesterol, triglyceride, and glucose level. No difference in any parameters was observed in haloperidol-treated patients (Krakowski *et al.*, 2009). Olanzapine was compared with second-generation antipsychotics risperidone in the effectiveness study. It was designed as a double-blinded trial with 339 schizophrenia patients randomly assigned into 2 groups in a 1:1 ratio to receive treatment with either olanzapine 10 to 20 mg/day or risperidone 4 to 12 mg/day. After the 28-week period study, within both treatment groups, mean weight changed from baseline to endpoint was statistically significant ($p<0.001$), but between treatment groups, olanzapine-treated patients experienced significantly greater weight gain than risperidone-treated patients (4.1 kg versus 2.3 kg; $p=0.015$) (Tran *et al.*, 1997). There were clinical study investigated the safety and tolerability of olanzapine in cancer related cachexia patients. First, olanzapine was evaluated in 30 patients with advanced cancer, started at a low dose of 2.5 mg and increased to 5, 7.5, 10, 12.5 mg with a maximum dose of 15 mg as 6 patients per cohort. Weight, mini-nutritional assessment (MNA), serum metabolic and inflammation factors were evaluated bi-monthly. There were 14 patients referred to the phase I study that had been enrolled at 2.5, 5 and 7.5 mg/day. Effects on weight gain were observed at 2 weeks in 6 patients. Drowsiness was observed in 3 patients and there was only one reported-event of grade 2 hepatitis. There was no correlation between the dose and toxicity (Braiteh *et al.*, 2008). In another clinical trial determine the effectiveness of megestrol acetate (MA) (which appears to be the standard and the most commonly used medicine for patient suffered from cancer-related anorexia), compared with the combination of MA and olanzapine (OLN). They randomly assigned 80 adult patients with advanced gastrointestinal cancer or lung cancer (stages III and IV) related anorexia to receive MA 800 mg daily or MA 800 mg plus OLN 5 mg daily for a period of 8 weeks. Patients were evaluated weekly using the M.D. Anderson Symptom Inventory (MDASI) with specific measurement of weight, appetite, nausea, and quality of life (QOL) measures. The MDASI symptom scores were calculated and analyzed at 4 and 8 weeks. The improvement in weight, appetite, nausea, and QOL at 4 and 8 weeks in patients receiving MA and MA plus OLN are shown in Figure 2. There were no significant changes in the scores in MA-treated group. The signifi-

cant improvement in appetite, nausea, general activity, mood, work, walking, and enjoyment was observed in both the MA and OLN group (Navari *et al.*, 2010). The summary results of olanzapine clinical studies are presented in table 2.

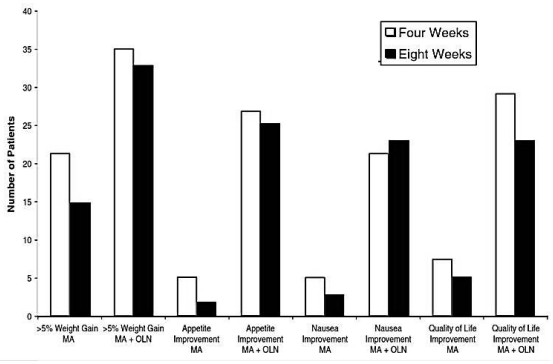

Figure 2 Effects of megestrol acetate (MA; n=37) and MA plus olanzapine (OLN; n=39) on cancer-related anorexia (Navari *et al.*, 2010)

Table 2 Summary of olanzapine clinical trials: safety, efficacy and weight gain effect (Navari and Marie, 2010; Bruce *et al.*, 2001; Tollefson *et al.*, 1997; Tran *et al.*, 1997; Krakowski *et al.*, 2009; Braiteh *et al.*, 2008).

Study design	Condition	Intervention (n)	Study period	Outcome	P Value	References
Retrospective - OLN - HAL	Weight gain in schizophrenia	OLN (573) HAL (103)	≥ 39 weeks	OLN = 6.26 kg[a] HAL = 0.69 kg[a]	p<0.001	Bruce, *et al.* (2001)
Prospective Randomized - OLN - HAL	Weight gain in schizophrenia	OLN (1336) HAL (660)	6 weeks	OLN = 1.88 kg[a] HAL = 0.02 kg[a]	p<0.001	Tollefson, *et al.* (1997)
Prospective double-blind - OLN - RIS	Weight gain in schizophrenia	OLN (166) RIS (165)	28 weeks	OLN = 4.1 kg[a] RIS = 2.3 kg[a]	p<0.015	Tran, *et al.* (1997)
Randomized double-blind - CLO - OLN - HAL	Weight gain in schizophrenia	CLO (37) OLN (37) HAL (36)	12 weeks	CLO = 2.36 kg[a] OLN = 3.59 kg[a] HAL = -2.0 kg[a]	OLN-CLO; p=0.41, OLN-HAL; p<0.001	Krakowski, *et al.* (2009)
Phase I pilot - OLN 2.5, 5, 7.5 mg	Weight gain in Advanced cancer	OLN (14)	2 weeks	Weight gain in 6 patients[b]	n.a.	Braiteh, *et al.* (2008)
Randomized-open label - MA - MA+OLN	Weight gain in GI and lung advanced cancer	MA (37) MA + OLN (39)	4 weeks 8 weeks	MA = 21/37[c] MA+OLN = 35/39[c] MA = 15/37[c] MA+OLN = 33/39%[c]	n.a. n.a.	Navari, *et al.* (2010)

SD = significant difference, CLO = Clozapine, HAL = Haloperidol, MA = Megestrol acetate, OLN = Olanzapine, RIS = Risperidone, n.a. = not applicable

[a] For mean weight gain of group, [b] not define term of measurement, [c] number of patient with weight improvement (greater than or equal to 5% weight gain)

Discussion and conclusion

Evidence from several clinical trials suggest that olanzapine, a new generation antipsychotic, is more effective and safer than older drugs and significantly increases weight gain in patients with schizophrenia (Ann and Linmarie, 2010). There were more side effects in haloperidol-treated group compared with OLN-treated group.

For cancer-related cachexia, olanzapine directly increases weight particularly lipid mass by preventing emesis and stimulating appetite. Olanzapine was evaluated in a phase I pilot study by Braiteh and colleagues (Braiteh *et al.*, 2008). The 7.5 mg per day doses increased body weight and improved nutritational status with few adverse events; however, the trial is still ongoing recruiting more subjects to determine the optimum dosage (National Institute of Mental Health; University of Virginia, 2012). A study comparing the effectiveness of megestrol acetate and the combination of olanzapine and megestrol acetate in patients with advanced gastrointestinal or lung cancer showed a significant improvement in weight, appetite, nausea, and QOL at 4 weeks and persisted at 8 weeks. Even though the study was randomized, it was not blinded, and a placebo effect could bias the result (Navari and Marie, 2010).

Olanzapine may be a good option for cancer-related cachexia patients by stimulating appetite, reducing nausea and decreasing metabolic rate (off-label). According to the current data, no conclusion could be drawn that it is better than other older agents in treating cancer-related cachexia. Nonetheless, it showed promising results and might give some hope to advanced cancer patients.

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