Sick Sinus Syndrome and Acute Tumor Lysis Syndrome after Low-dose Thalidomide Therapy in Recurrent Hepatocellular Carcinoma：A Case Report

Ming-Chieh Tsai[1], Yee Chao[6], Chia-Long Lee [2], Yi-Ann Chen[3], Yen-Yu Lu[4], and Jui-Neng Yang[1,5]

[1]Divisions of Gastroenterology, [3]Nephrology and
[4]Cardiology, Cathay General Hospital, Sijhih;
[2]Division of Gastroenterology, Cathay General Hospital, Taipei;
[5]Ching-Kuo Institute of Management and Health, Keelung, Taiwan;
[6]Cancer center, Taipei Veterans General Hostipal

Abstract

Thalidomide has immunomodulatory and anti-angiogenic properties of potential value in anti-cancer therapy. The drug has been used in clinical trials for salvage treatment in advanced, unresectable hepatocellular carcinoma (HCC). These have been demonstrated that thalidomide has 3%-6% of partial response rate and stabilize the disease in 16-31% of HCC. Further, thalidomide treatment is generally tolerable, with side effects only necessitating cessation of therapy in 20% of cases. One of severe toxic effects is symptomatic bradycardia, mostly reported in therapy for multiple myeloma (MM)(1%-6%) but never in HCC. Tumor lysis syndrome (TLS) in treating both MM and HCC is an another life threatening complication that reported sporadically. Herein, we report a case involving sick sinus syndrome and acute tumor lysis syndrome after15 days of low-dose thalidomide therapy (100 mg/d). This case highlights the need for close monitoring of the signs and symptoms of bradycardia and electrolytes at the commencement of thalidomide therapy.(J Intern Med Taiwan 2008; 19: 536-541)

Key Words： Hepatocellular carcinoma, Tumor lysis syndrome, Sick sinus syndrome, Thalidomide

Introduction

Hepatocelluar carcinoma (HCC) is the leading cause of cancer death in Taiwan, however, most of the HCC are already incurable at the time of diagnosis. Thalidomide salvage therapy offers some benefits in the treatment of unresectable HCC(1-7). Further, side effects are generally tolerable, with cessation of therapy only necessary in a minority of patients. The most severe toxic effects are symptomatic bradycardia and tumor lysis syndrome, mostly reported in therapy for multiple myeloma but rarely in HCC(8-11). Herein,

Correspondence and reprint requests to：Dr. Jui-Neng Yang
Address :Division of Gastroenterology, Cathay General Hospital, Sijhih, No.2, Lane 59, Jiancheng Rd., Sijhih City, Taipei County 221, Taiwan.

we report a case of unresectable HCC treated using low-dose thalidomide, complicated by tumor lysis and sick sinus syndromes. These rare complications are life threatening, and immediate therapy is required. The presented case highlights the need for close monitoring of the signs and symptoms of bradycardia and electrolytes at the commencement of thalidomide therapy.

Case Report

The 81-year-old female patient was a victim of chronic hepatitis C infection and HCC. She had undergone transcatheter arterial chemoembolization (TACE) 2 years prior to her most recent admission. On physical examination, the patient had one buldging mass over right upper quadrant of abdomen, ascites and leg edema. The rest examination was unremarkable. Blood test results were AST: 193 IU/L, ALT: 68 IU/L (Normal range (NR): 5-35 IU/L), bilirubin (total):1.0 mg/dL(NR: 0.2-1.5 mg/dL),BUN: 14 mg/dL (NR: 8-25 mg/dL), creatinine :0.7 mg/dL (NR: 0.5-1.5 mg/dL), albumin: 3.2 g/dL (NR:3.5-5.5 g/dL), ammonia: 33 umol/L (NR: 9-33 umol/L), sodium level : 132 mmol/L (NR: 135-145 mmol/L), potassium level: 4.2 mmol/L (NR: 3.5-5.3 mmol/L), white blood cell counts : 6.57 x 10^3 (4-10 x 10^3), hemoglobin: 10.4 g/dL (NR: 12-16 g/dL), hematocrit: 31.3 % (NR: 37-47 %), platelet counts: 229 x 10^3 / μL (NR: 130-400 x 10^3 / μL).

A review of her medical history revealed many years of treatment with calcium-channel blockers (lercanidipine 10 mg once daily), angiotension II receptor antagonists (telmisartan 40 mg once daily) and thiazide diuretics (indapamide 1.5 mg once daily) for hypertension. Previous electrocardiogram (ECG) and coronary angiography had demonstrated normal sinus rhythm and a patent coronary artery on March 26, 2007 for her chest pain. Additionally, she had been subsequently started on two diuretics (furosemide 20 mg once daily and spironolactone 50 mg once daily) for her ascites since April 24 2007.

Multiple recurrent HCC was demonstrated in both lobes of the liver from tri-phase contrast-enhanced abdominal computed tomography (CT); the largest structure was about 11 cm (Fig. 1). The alpha-fetoprotein level was 113 ng/ml (NR: 0-10 ng/ml). The tumors were evaluated as unresectable and, as the patient refused intensive treatment,

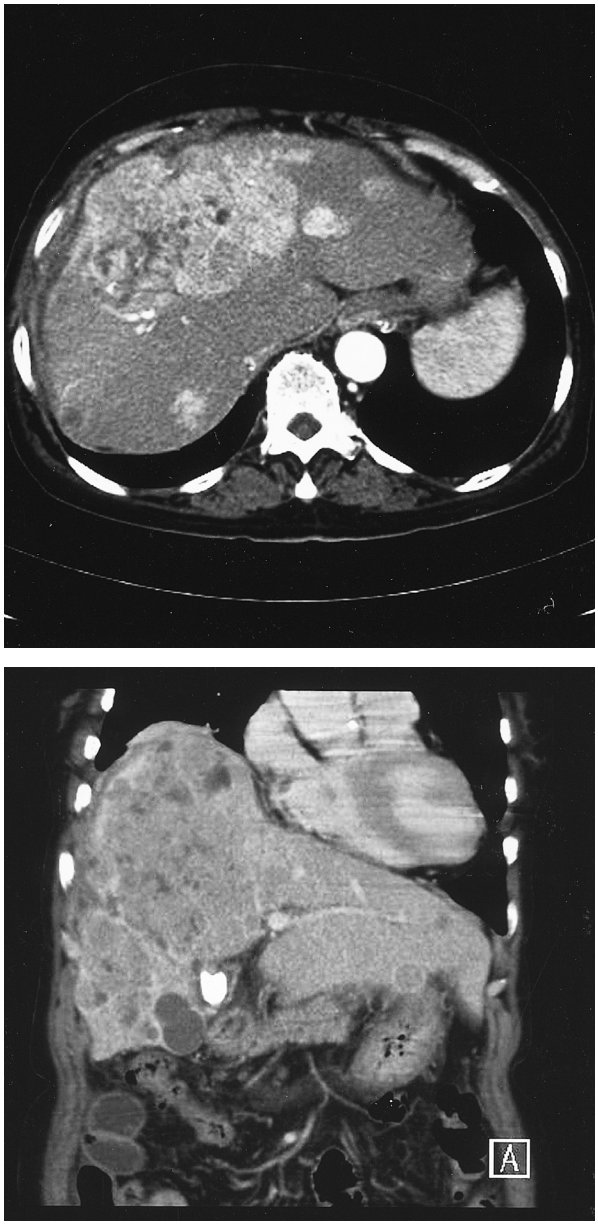

Fig.1.computed tomography (CT) demonstrated multiple liver tumors in both lobes of the liver (late arterial phase), the largest one was about 11cm in size.

salvage thalidomide therapy (50 mg at night) was started on April 25, 2007, with the dose doubled from day 11 (100 mg at night).

On the fifteenth day of thalidomide therapy, the patient suffered epigastric pain with radiation to back, dizziness, chest tightness and shortness of breath and was brought to the emergency department. ECG showed junctional rhythm with a heart rate of 28 beats/min (Fig. 2). Hypotension (blood pressure 80/40 mmHg) was also noted. Under the impression of sick sinus syndrome (SSS), she was admitted to the intensive care unit for urgent resuscitation and insertion of a temporal pacemaker.

A blood test showed: potassium level: 7.1 mmol/L, sodium level: 127 mmol/L , uric acid level: 11.1 mg/dL(NR: 2.5-6.3 mg/dL), phosphorus level: 5.9 mg/dL(NR: 2.5-4.5 mg/dL), lactate dehydrogenase level: 2327 IU/L(NR: 95-215 IU/L) and serum creatinine: 1.7 mg/dL, and an arterial blood gas showed metabolic acidosis: PH of 7.295 (NR: 7.35-7.45), PaCO2 of 28.8 mmHg(NR: 35-45 mmHg), PaO2 of 106.6 mmHg (NR: 83-108 mmHg), $HCO3^-$ of 13.7 meq/L (NR: 21-28 meq/L), O2 saturation: 97.5%. Tumor lysis syndrome (TLS) was also diagnosed at this time. There was no significant change of tumor size found on a following sonography. Symptomatic treatment included furosemide, allopurinol, antihyperkalemic agents (resonium-A; sodium polystyrene sulfonate), and alkalinazation, were started. The lercanidipine, spironolactone, indapamide, and telmisartan were stopped, but the thalidomide (100 mg at night) was continued. After 2 days on the new treatment, the laboratory data revealed a improvement for most results: sodium level: 129 mmol/L, potassium level: 4.5 mmol/L, creatinine : 1.3 mg/dL, lactate dehydrogenase: 1392 IU/L. An arterial blood gas showed a PH of 7.378 , $HCO3^-$ of 22.1 meq/L. The heart rate also resuming normal sinus rhythm on a series of following ECG. By the fourth day, the

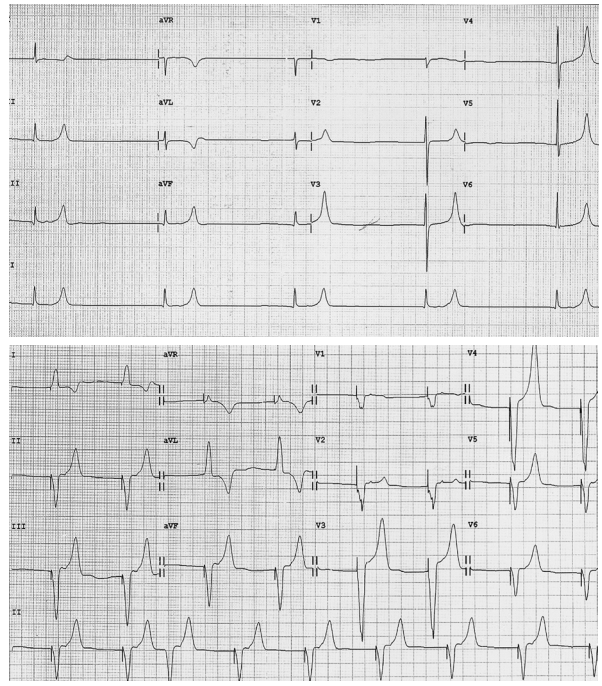

Fig.2.Junctional rhythm, heart beat:28/min (upper), After temporal pacemaker implantation (bottom).

potassium level had dropped to 2.6 mmol/L, so the furosemide was stopped and added potassium citrate. The pacemaker was removed on the seventh day of hospitalization. The patient was discharged on the eleventh day post admission with normal sinus rhythm and a heart rate of 80-90 beats/min after pacemaker removal, with a normal potassium level of 4.3 mmol/L. The diurectic agents were subsequently replaced with furosemide (40 mg twice daily) and spirolactone (50 mg once daily).

Unfortunately, three days later, she was again sent to the emergency room for chest tightness and dizziness without shock (BP: 136/46 mmHg). ECG showed sinus bradycardia (heart rate 37 beats/min), with blood examination showing sodium level: 121 mmol/L and potassium level: 5.6 mmol/L. The patient refused pacemaker insertion, so she was treated with antihyperkalemic agents (resonium-A), 3% normal saline, and atropine injection (total 2mgs). Under the suspicion of thalidomide related bradycardia, the thalidomide was stopped. The heart rhythm returned to normal sinus rhythm

the next day.

At the writing, the patient's sinus rhythm and electrolyte levels were normal, and she was being maintained on furosemide (40 mg twice daily) and amlodipine (5 mg once daily).

Discussion

HCC is one of the most common cancers worldwide. HCC therapy is difficult because 80% of cases involve decompensated cirrhosis. Liver cirrhosis makes the tumor unresectable. Further, the response to chemotherapy and radiotherapy is characteristically poor. TACE can improve survival rate; however, reserved liver function also remains a limitation. Thalidomide is a new, salvage therapeutic modality for HCC [1,2].

Thalidomide has antiangiogenic effects by blocking the activity of angiogenic cytokines, such as vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF) and also has immunomodulation of cytokines, particularly tumor necrosis factor-alpha (TNF-α). These properties offer potential in anti-cancer therapies. Its efficacy has been investigated particularly for erythema nodosa leprosum (ENL), multiple myeloma(MM) [2,12-15].

HCC is a hypervascular tumor which overexpresses VEGF. Thus, thalidomide appears to be feasible as a treatment for HCC. In 2000, Patt et al., first reported a case where thalidomide treatment was used to shrink a HCC[16]. Many phase II studies are ongoing. Overall response rate among the previous studies, thalidomide as a single medication, ranges for partial response and disease stabilization of 3-6% and 16-31% were achieved at a dosage range of 100-1000 mg/day[1-7]. Those reports reveal thalidomide monotherapy offers tolerable antitumor activity in advanced HCC.

The common side effects of thalidomide include drowsiness, sedation, constipation, rash and paresthesiae. Dizziness, hypotension, deep vein thrombosis and bradycardia occur less commonly [8-9,12]. The incidence correlates with dose and duration of therapy. The toxicity was higher in patients receiving more than 400 mg/d and 6 months of thalidomide. Adverse effects severe enough to necessitate cessation of therapy are seen in around 20% of patients [13]. TLS is a rare and life threatening complication in patients with MM treated with thalidomide and it has been sporadically reported [10,11]. The treatment of HCC-related TLS has not been reported, with only one Taiwanese case reported advanced HCC with fatal TLS after treatment to a maximum of 300 mg/day for a total of 2 weeks[19]. In another Spanish report, 3 days of thalidomide treatment (200 mg/d) induced TLS in one patient with MM[11]. In the presented case, TLS occurred despite a very low dose of thalidomide (maximum 100 mg/d) and a very short treatment course (total 15 d).

As a monotherapy, thalidomide-associated sympatomatic bradycardia is another rare, severe toxic effect and the post-marketing surveillance reported the incidence is 0.12%[18]. The incidence is high especially in cases of multiple myeloma (mild 25%, severe 1-6%)[21-23].The toxicity increases when the drug is combined with dexamethasone or other chemotherapy drugs. Fahdi et al. reported the overall incidence of thalidomide combined chemotherapy associated bradycardia (heart rate $<$ 60 beats / min) is 53% and symptomatic bradycardia is high (about 19%) in treating MM. Most of these patients relieved symptoms after reducing the thalidomide dose and only 2.5% of the patients required pacemaker implantation[9]. Although the mechanism remains unknown, Clark et al., have suggested that it could be related to the central sedative effect of thalidomide[18]. Many reports have emphasized the fact that concurrent medications (e.g., toxicity related to calcium channel or beta adrenergic receptor blockade) may affect heart rate and thereby

increase the risk of thalidomide-induced bradycardia[17,18]. Hyperkalemia as a result of TLS, especially if severe, is another cause of cardiac rhythm pathologies. Sinus arrest of sudden onset is more likely to occur when the potassium level is very high (e.g., ＞8 mmol/L), however, concomitance with negative chronotropic drugs may occur even with moderate hyperkalemia[20]. Thalidomide-associated SSS in HCC has never been reported in the literature. In our case, the cause of the first SSS episode may have been multifactorial. In the second episode of symptomatic bradycardia may have been more directly related to thalidomide complication.

In conclusion, in combination with SSS and TLS occurring soon after commencement of low-dose thalidomide treatment for HCC has never been reported in the literature. Many concurrent medications affecting the heart rate and severe hyperkalemia may increased the risk of thalidomide-induced bradycardia. This case report highlights the need for close monitoring of the signs and symptoms of bradycardia and electrolyte levels at the beginning of thalidomide therapy, even at very low dosages and short courses.

References

1.Chiou HE, Wang TE, Wang YY, Liu HW. Efficacy and safety of thalidomide in patients with hepatocellular carcinoma. World J Gastroentol 2006; 12: 6955-60.
2.Wang TE, Kao CR, Lin SC, et al. Salvage therapy for hepatocellular carcinoma with thalidomide. World J Gastroentol 2004; 10: 649-53.
3.Lin AY. Brophy N, Fisher GA, et al. Phase II study of thalidomide in patients with unresectable hepatocellular carcinoma. Cancer 2005; 103: 119-25.
4.Chuah B, Lim R, Boyer M, et al. Multi-centre phase II trial of thalidomide in the treatment of unresectable hepatocellular carcinoma. Acta Oncol 2007; 46: 234-8.
5.Hsu C, Chen CN, Chen LT, Wu CY, et al. Low-dose thalidomide treatment for advanced hepatocellular carcinoma. Oncology 2003; 65: 242-9.
6.Patt YZ, Hassan MM, Lozano RD, et al. Thalidomide in the treatment of patients with hepatocellular carcinoma: a phase II trial. Cancer 2005; 103: 749-55.
7.Han SH, Park SH, Kim JH, et al. Thalidomide for treating metastatic hepatocellular carcinoma: a pilot study. Korean J Intern Med 2006; 21: 225-9.
8.Lopez-de la, Cruz I, Aguayo-Gonzalez A, Lopez-Karpovitch X. Thalidomide-associated bradycardia in patients with hematologic disease: a single institution experience. Rev Invest Clin 2005; 58: 424-31.
9.Fahdi IE, Gaddam V, Saucedo JF, et al. Bradycardia during therapy for multiple myeloma with thalidomide. Am J Cardiol 2004; 93: 1052-5.
10.Cany L, Fitoussi O, Boiron JM, et al. Tumor lysis syndrome at the beginning of thalidomide therapy for multiple myeloma. J Clin Oncol 2002; 20: 2212.
11.N. Fuente, J.M. Mane, R. Barcelo, et al. Tumor lysis syndrome in a multiple myeloma treated with thalidomide. Ann Oncol 2004; 15: 537.
12.Altintas A, Ayyildiz O, Atay AE, Cil T, Isikdogan A, Muftuoglu E. Thalidomide-associated arterial thrombosis: two case reports. Ann Acad Med Singapore 2007; 36: 304-6.
13.Singhal S, Mehta J. Thalidomide in cancer. Biomed Pharmacother 2002; 56: 4-12.
14.Politi PM. Thalidomide. Clinical trials in cancer. Medicina 2000; 60: 61-5.
15.Scott Wadler. Thalidomide for advanced hepatocellular carcinoma. Cancer 2005; 103: 1-4.
16.Patt YZ, Hassan MM, Lozano RD, Ellis LM, Peterson JA, Wangh KA. Durable clinical response of refractory hepatocellular carcinoma to oral administered thalidomide. Am J Clin Oncol 2000; 23: 319-21.
17.Kaur A, Yu SS, Lee AJ, Chiao TB. Thalidomide-induced sinus bradycardia. Ann Pharmacother 2003; 37: 1040-3.
18.Clark TE, Edom N, Larson J, Lindsey LJ. Thalidomide capsules.A review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. Drug Saf 2001; 24: 87-117.
19.Lee CC, Wu YH, Chung SH, Chen WJ. Acute tumor lysis syndrome after thalidomide therapy in advance hepatocellular carcinoma. Oncologist 2006; 11: 87-8.
20.Bonvini RF, Hendiri T, Anwar A. Sinus arrest and moderate hyperkalemia. Ann Cardiol Angeiol (Paris) 2006; 55: 161-3.
21.Rajkumar SV, Gertz MA, Lacy MQ, et al. Thalidomide as initial therapy for early-stage myeloma. Leukemia. 2003; 17: 775-9.
22.Kumar S, Gertz MA, Dispenzieri A, et al. Response rate, durability of response, and survival after thalidomide therapy for relapsed multiple myeloma. Mayo Clin Proc. 2003; 78: 34-9.
23.Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. J.Supportive Oncol 2003; 1: 194-205.

以低劑量沙利竇邁(Thalidomide)治療肝癌併發竇性緩脈和急性腫瘤溶解症：一病例報告

蔡明杰[1] 趙毅[6] 李嘉龍[2] 陳怡安[3] 盧彥佑[4] 楊瑞能[1,5]

國泰綜合醫院汐止分院 [1]腸胃內科 [3]腎臟內科 [4]心臟內科
[2]國泰綜合醫院 腸胃內科
[5]經國健康管理學院 [6]台北榮民總醫院 癌症中心

摘 要

沙利竇邁(thalidomide)已在臨床上用於肝癌末期患者，據文獻報告有3%-6%部份反應率和 16%-31%患者可穩定病情，但也有 20%患者因副作用而停藥，較嚴重副作用是有症狀之緩脈和急性腫瘤溶解症，有症狀之緩脈多好發於治療多發性骨髓瘤患者，發生率約1%-6%，未見於肝癌患者，而因使用沙利竇邁治療肝癌末期患者發生急性腫瘤溶解症僅有一例報告，在此，我們報告一例 81歲肝癌末期患者只接受短期(15天)和低劑量(100mg/天)沙利竇邁治療後便產生嚴重竇性緩脈和急性腫瘤溶解症，本文提出在使用沙利竇邁治療肝癌患者初期應監測心跳，肝腎功能和電解質。