Recombinant Interferon-Alpha 2b and Megestrol Acetate in Patients with Advanced Renal Cell Carcinoma

NARIN VORAVUD, M.D.*,
VIROJ SRIURANPONG, M.D.*,
PRASERT LERTSAGUANSINCHAI, M.D.*

Abstract

Fifteen patients with histologically proven metastatic or unresectable renal cell carcinoma were enrolled for a phase II trial of Interferon-alpha 2b ($\geq 6 \times 10^6$ U/m^2) plus megestrol acetate (160 mg/day). A response rate of 14.3 per cent was achieved in this study. We observed weight gain (median 3.2 kilogram; range 1.1 to 6.9) in 5 patients, and stable weight in 5 of the 14 patients who completed the protocol. Weight gain occurred regardless of extent of metastasis or response to interferon. Our data suggest a possible role for megestrol acetate in alleviating anorexia and weight loss in patients with renal cell carcinoma undergoing interferon treatment. Further clinical trials are clearly warranted.

Key words : Interferon, Megestrol Acetate, Anorexia, Kidney Neoplasms

VORAVUD N, et al
J Med Assoc Thai 2000; 83: 123-128

The response to treatment of patients with metastatic or unresected renal cell carcinoma has been disappointing. Chemotherapy, hormonal therapy, immunologic manipulations and other modalities have failed to improve survival in these patients[1]. Hormonal therapy, mostly progestational agents, produces an overall response less than 15 per cent[2]. Recently, interferon-alpha has been shown to produce response rates ranging from 4 per cent to 26 per cent in advanced renal cell carcinoma[3-11]. Although, the response to interferon is promising, its therapeutic benefit is limited by its toxicity, which frequently leads to dose reduction and early discontinuation of treatment. Some of the typical side effects seen with interferon such as fatigue, anorexia, weight loss, and anemia may be directly opposed by effects seen with megestrol acetate: improved mood and sense of well being, increased appetite with catabolic weight gain, and increased hematocrit[12].

* Medical Oncology Unit, Department of Medicine and Radiotherapy Unit, Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Our study was designed to determine whether the addition of megestrol acetate to interferon therapy in metastatic or unresectable renal cell carcinoma could improve either the response rate to or patient tolerance of interferon therapy.

MATERIAL AND METHOD

Patient Eligibility

All subjects had histologically proven metastatic or unresectable renal cell carcinoma. To be eligible for this study, a patient had to be at least 18 years of age, and to have measurable disease, a Karnofsky performance status $\geq$ 60 per cent or Zubrod $\leq$ 2, a life expectancy >12 weeks, an absolute granulocyte count >1,500, a platelet count >100,000, bilirubin <1.5 mg/dl, SGPT less than four times the upper limit of normal, creatinine <1.5 mg/dl, calcium <10.5 mg/dl. The patient may have undergone a maximum of two prior systemic therapies. Patients with brain metastases were eligible provided other measurable disease existed and brain lesions had been controlled for six months (required no therapy during the study) and were not life threatening. While enrolled in the study, patients could receive no other therapy directed at their tumor. Patients were not eligible if they had no measurable disease; active angina, severe coronary artery disease, a history of thromboembolic disease, or other serious intercurrent medical illness were also grounds for exclusion. Patients who had received progestational agents or interferon were ineligible. In addition, patients were not eligible if they had chemotherapy, immunotherapy, hormonal therapy or radiotherapy up to 3 weeks before entry into the study (6 weeks from mitomycin C or nitrosourea) and had to be fully recovered from acute toxic effects of prior chemotherapy. All patients signed an informed consent that met all institutional, state and federal guidelines.

Treatment

Pretreatment evaluation included history and physical examination, body weight measurement, performance status assessment, and the following diagnostic tests: CBC with differential and platelet count, complete blood profile, HIV antibody, hepatitis B surface antigen, prothrombin time, partial thromboplastin time, urinalysis, chest X-ray, electrocardiogram, computed tomography, and magnetic resonance imaging or appropriate nuclear scans for metastatic sites. History, physical examination, and chest X-ray were obtained before and monthly after treatment began. Body weight was measured during each visit. CBC with differential and platelet count were checked weekly for the initial 12 weeks, and then every 4 weeks thereafter. Blood profile and urinalysis were repeated every other week for the initial 12 weeks, and then every 4 weeks thereafter. If computed tomograms, magnetic resonance tomograms, or bone scans were required, these were repeated every 2 months.

Patients received interferon subcutaneously three times weekly. The initial dose of interferon-alpha 2b (Intron-A, Schering-Plough), $3x10^6$ U/m^2, was escalated to $6x10^6$ U/m^2 on day 8 and $9x10^6$ U/m^2 on day 15. Only those patients who tolerated $\geq$ $6x10^6$ U/m^2 subcutaneously three times a week for more than 8 weeks were continued on the study. Patients also received megestrol acetate (Megace, Bristol-Meyers Oncology Division, Evansville, IN) 160 mg orally per day beginning on day 1. The treatment was given until there was evidence of disease progression or as long as doses of interferon $\geq$ $6x10^6$ U/m^2 three times a week could be tolerated. Interferon doses were decreased to $6x10^6$ U/m^2 in patients who had grade 4 toxic reactions. Patients who developed grade 3 toxic reactions continued on this study as long as the total weekly dose remained $\geq$ $6x10^6$ U/m^2 three times a week. Megestrol acetate would be discontinued in cases of weight gain more than 10 per cent of baseline, or the development of thromboembolic disease or clinically significant congestive heart failure not responsive to diuretices. This did not occur in any of the 14 patients.

Assessment of Response to Treatment

Complete response was defined as the absence of any detectable tumor mass for a minimum of 4 weeks. Partial response was defined as a 50 per cent or greater reduction in the sum of the products of perpendicular diameters of measurable lesions for a minimum of 4 weeks. Minor response was defined as lesion-size reduction of greater than 25 per cent but less than 50 per cent. Stable disease was defined as change of less than 25 per cent in measurable lesions and the absence of new lesions. Progressive disease was defined as unequivocal increase of more than 25 per cent in size of measurable lesions or the appearance of new lesions.

Table 1. Patient characteristics.

Number	14
Males/Females	12/2
Median age (Range)	58 (45-67)
Prior treatment	
Nephrectomy	8
Radiotherapy	2
Chemotherapy	1
None	3
Performance status (Zubrod scale)	
0	5
1	8
2	1

RESULTS

Fifteen patients were entered in the study. Of these, one patient was found to be ineligible and was taken off the study after 1 week of treatment because of rapid deterioration of his liver function. Pretreatment characteristics of the 14 patients who remained in this study are shown in Table 1.

Two patients achieved a complete remission in metastatic pulmonary lesions (cases 3 and 7 response rate 14.3%). In addition to these two responders, one patient had a minor response (case 1). One patient (case 7) relapsed after his initial complete remission and went into a second complete remission after 5-FU, interferon and megestrol acetate. The duration of the first and the second complete remission were 6 months and 8 months respectively.

Weight gain from megestrol acetate was seen in 6 of the 14 patients (42.9%) the median maximum weight gain of 3.2 kilogram (range 1.1 to 6.9 kg). Four patients maintained a stable weight. Only one patient had weight loss of more than 10 per cent (Table 2). No patient had significant change in albumin level during the treatment.

Treatment was well tolerated (Table 3). Two patients required a dose reduction to $6x10^6$ U/m^2 because of fatigue, but one later tolerated dose escalation back to $9x10^6$ U/m^2. No hematologic side effects from interferon were seen in any of these patients. The karnofsky performance status was unchanged in all patients during the treatment. Only one patient was taken off the study after less than 12 weeks treatment because of rapidly progressive disease.

DISCUSSION

The role of hormones in renal cancer is supported by both experimental study and several clinical trials. Estrogens can induce renal adenocarcinoma in Syrian golden hamsters[13]. Induction of primary renal tumors by estrogen and growth of transplanted estrogen-induced renal cell carcinoma are both inhibited by progesterone[14,15]. Of 272 collected cases of metastatic renal cancer from various reports (between 1964 and 1971) in which

Table 2. Patient response and maximal weight change during interferon and megestrol acetate treatment.

Patient number	Age	Metastatic sites	Response	Weight During treatment KG (%)	Change After treatment KG (%)
1	65	Lung, Liver	MR	+6.9(+9.1)	-2.2(-2.5)
2	45	Lung, Liver	PD	-11.6(-11.2)	-12.5(-12.1)
3	58	Lung	CR	-3.6(-5.4)	-6.39(-9.8)
4	63	Lung	PD	0 (0)	0 (0)
5	60	Bone	PD	+1.1(+1.5)	-1.1(-1.5)
6	46	Lung	PD	-1.1(+1.5)	-4.85(-5.3)
7	66	Lung	CR	-3.8(-3.3)	-6.3(-5.6)
8	55	Lung	PD	+3.2(+3.2)	-10(-9.6)
9	67	Bone	PD	0 (0)	-1.1(-1.4)
10	58	Lung	PD	0 (0)	-8.6(-10.4)
11	50	Lung	PD	0 (0)	-0.7(-0.6)
12	63	Lung, Liver	PD	+1.4(+1.8)	ND
13	46	Lung	PD	0 (0)	0 (0)
14	49	Lung Liver	PD	-1.2(-1.6)	-1.3(-1.7)

MR = Minimal Response; PD = Progressive Disease; CR = Complete Response; ND = not done

Table 3. Toxicities of the combination of interferon and megestrol acetate.

Toxic reactions	Number of patients				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Flu-like symptoms	8	6	0	0	14
Fatigue	4	5	2	0	11
Anorexia	2	0	0	0	2
Nausea/Vomiting	0	1	0	0	1
Tremor	1	0	0	0	1
Pain	1	3	0	0	4
Dyspnea	3	0	0	0	3
Neutropenia	3	1	0	0	4
Thrombocytopenia	0	0	0	0	0
Anemia	2	0	0	0	2
Proteinuria	4	3	0	0	7
Increased SGPT	1	2	0	0	3
Increased alkaline phophatase	1	1	0	0	2
Increased lactate dehydrogenase	2	2	0	0	4

patients treated with progestins or androgens, the overall objective response rate was 15 per cent, (range 6 per cent to 33 per cent[16]. However, subsequent reports showed no significant activity of megestrol acetate in this disease[17]. In a randomized study of 60 patients with advanced renal cell carcinoma treated with either interferon or medroxyprogesterone acetate, there was no difference in clinical response and survival between the two treatment arms[18]. In our study, the response to interferon combined with megestrol acetate in metastatic renal cell carcinoma is not superior to that obtained with interferon or hormonal treatment alone. This indicates that there is no synergy between interferon and megestrol acetate at the doses used in this study.

The clinical usefulness of interferon is limited by its toxicity. Among 1,403 patients who received interferon, treatment was discontinued in 153 patients (11%) because of adverse side effects [19]. Our patients tolerated the treatment well. Daily doses of more than 10 million IU result in significant weight loss in most patients[20]. Weight gain has been reported in 20 per cent to 30 per cent of patients with a variety of tumors receiving megestrol acetate at a conventional dose (160 mg/d)[21]. Our data suggest that megestrol acetate is useful in alleviation of interferon-induced weight loss. Our data further suggest that megestrol acetate is capable of inducing weight gain in patients with advanced renal cancer irrespective of response to interferon therapy or progression of disease (Table 2). However, since anthropometric measurements were not evaluated in this study, it is uncertain which body compartment was responsible for the increase in weight. Given that no patients developed edema or glucocorticoid effect, and that serum albumin remained stable, it is likely that an increase in appetite and acquisition of body mass contributed to weight gain in this study.

The mechanisms of weight gain from megestrol acetate remain unknown but patients report a significant increase in appetite and the increased weight does not appear to be secondary to fluid retention[17]. Megestrol acetate is a potent inducer of conversion of Swiss 3T3-L1 mouse fibroblast cell line into adipocytes. It is speculated that the conversion of fibroblasts to adipocytes and the accumulation of intracellular lipids also are stimulated by megestrol acetate *in vivo*[22]. A physiologic basis for cancer cachexia has been recently proposed based on the action of tumor necrotic factor, a hormone produced by macrophage[23]. However, megestrol acetate failed to reverse the inhibitory effect of tumor necrosis factor on 3T3-L1 cell line[22].

Combined interferon-alpha 2b and megestrol acetate do not appear superior to interferon alone in the management of advanced renal cell carcinoma. The combination does improve patient tolerance to interferon treatment. The alleviation of interferon-induced weight loss is encouraging in this

study. The true benefit of megestrol acetate for interferon-related weight loss and its potential to improve tolerance of interferon treatment requires a prospective, randomized, placebo-controlled trial. Such a trial needs standardized methods of evaluating nutritional status, caloric count, appetite scale, relative change of weight, quality of life assessments; a larger number of patients is also needed. Additional studies will be necessary to clarify the role of megestrol acetate in combination with interferon and to establish optimal dose schedules for this combination.

(Received for publication on March 30, 1998)

REFERENCES

1. Linehan WM, Shiplely WU, Longo DL. Cancer of the kidney and ureter. Cancer Principles and Practices of Oncology 3rd ed. In DeVita VT Jr, Helman S, Rosenberg SA (eds): Philadelphia, J.B. Lippincott 1989: 979-1007.
2. Torti FM. Treatment of metastatic renal cell carcinoma. Recent results Cancer Res 1983;85: 123-42.
3. Quesada JR, Swanson DA, Trindade A, Trindade A, Gutterman JU. Renal cell carcinoma: Antitumor effects of leukocyte interferon. Cancer Res 1983; 43:940-7.
4. Krown SE, Einzig AI, Abramson JD, Oettgen MF: Treatment of advanced renal cell cancer with recombinant leukocyte A interferon. Proc Am Soc Clin Oncol 1983:2:58 (abstr).
5. deKernion JB, Sarna G, Figlin R, Linder A, Smith RB. The treatment of renal cell carcinoma with human leukocyte alpha-interferon. J Urol 1983; 130:1063-6.
6. Trump D, Harris J, Tuttle R, et al. Phase II trial of high dose human lymphoblastic interferon (Welferone) in advanced renal cell caricnoma (aRCC). Proc Am Soc Clin Oncol 1985;3:153 (abstr).
7. Kempf RA, Grunberg SM, Daniels JR, et al. Recombinant interferon alpha-2a (Intron A) in a phase II study of renal cell carcinoma. J Biol Respone Mod 1986;5:27-35.
8. Kirkwood JM, Haris JE, Vera R, et al. A randomized study of low and high doses of leukocyte alpha-interferon in metastatic renal cell carcinoma: The American Cancer Society Collaborative Trial. Cancer Res 1985;45:863-71.
9. Vurgrin D, Hood L, Taylor W, Laszlo J. Phase II study of human lymphoblastoid interferon in patients with advanced renal cell carcinoma. Cancer Treat Rep 1985;69:817-20.
10. Neidhart JA, Gagen MM, Young D, et al. Interferon-alpha therapy for advanced renal cell carcinoma. Cancer Res 1984;44:4140-3.
11. Marumo K, Murai M, Hayakawa M, et al. Human lymphoblastoid interferon therapy for advanced renal cell carcinoma. Urology 1984;24:567-71.
12. Aisner J, Tchekmedyian NS, Moody M, Tait N. High-dose megestrol acetate for the treatment of advanced breast cancer; dose and toxicities. Semi Hematol 1987;242:48-55.
13. Bloom HJG, Dukes CE, Mitchley BCV. Hormone dependent tumors of the kidney: I. The Oestrogen-Induced Renal Tumor of the Syrian Hamster; Hormone Treatment and Possible Relationship to Carcinoma of the Kidney in Man. Br J Cancer 1963;17:611.
14. Bloom HJG, Baker WH, Dukes CE, Mitchey BCV. Hormone-dependent tumors of the kidney: II. Effect of endocrine ablation procedures on the transplanted oestrogen-induced renal tumor of the Syrian hamster. Br J Cancer 1963;17:646.
15. Bloom HJG, Roe FJC, Mitchley BCV. Sex hormones and renal neoplasia. Cancer 1967;20:2118.
16. Bloom HJG. Hormone-induced and spontaneous regression of metastatic renal cancer. Cancer 1973;32:1066-71.
17. Steineck GH, Strander HB, Carbin E, et al. Recombinant leukocyte interferon alpha-2a and medroxyprogesterone in advanced renal cell carcinoma: A randomized trial. Acta Oncol 1990;29: 155-62.
18. Steineck GH, Strander H, Carbin Be, et al. Recombinant leukocyte interferon alpha-2a and medroxyprogesterone in advanced renal cell carcinoma: A randomized trial. Acta Oncol 1990;29:155-62.
19. Spiegel RJ. Alpha interferon: A clinical overview. Urology 1989;34:75-9.
20. Quesada JR, Talpaz M, Rios A, Kurzrock R, Gutterman JU. Clinical toxicity in cancer patients: A review. J Clin Oncol 1986;4:234-43.
21. Loprinzi CL, Ellison NM, Schaid DJ, et al. A controlled trial of megestrol acetate for the treatment ofcancer anorexia and cachexia. J Natl Cancer Inst 1990;82:1127-32.
22. Hamburger AW, Parnes H, Gordon GB, et al. Megestrol acetate induced differentiation of 3 T3-L1 adipocytes in vitro. Semin Oncol 1988;15(2 Suppl 1) 76-8.

23. Torti FM, Dieckmann B, Beutler B, Cerami A, Ringold GM. A macrophage factor inhibits adipocyte gene expression: A in vitro model of cachexia. Science 1985;229:867-9.

รีคอมบิแนนต์อินเตอเฟียรอน-อัลฟา 2บี และยามีเจสทรอลอาซีเตท ในผู้ป่วยมะเร็งไตที่เป็นมาก

นรินทร์ วรวุฒิ, พ.บ.,*
วิโรจน์ ศรีอุฬารพงศ์, พ.บ., ประเสริฐ เลิศสงวนสินชัย, พ.บ.**

ผู้ป่วยมะเร็งไตระยะแพร่กระจายหรือผ่าตัดไม่ได้จำนวน 15 คน ได้รับการรักษาด้วยยาอินเตอเฟียรอน-อัลฟา 2 บี ($\geq 6 \times 10^6$ หน่วยต่อตารางเมตร) ร่วมกับยามีเจสทรอลอาซีเตท (160 มิลลิกรัมต่อวัน) พบการตอบสนองต่อการรักษาร้อยละ 14.3 ผู้ป่วย 5 รายมีน้ำหนักเพิ่มขึ้น (ค่ามัธฉิม 3.2 กิโลกรัม, ระยะ 1.1 ถึง 6.9) และผู้ป่วย 5 รายใน 14 รายมีน้ำหนักคงที่ ข้อมูลจากการศึกษานี้แสดงถึงฤทธิ์ของยามีเจสทรอลอาซีเตท ในการลดอาการเบื่ออาหารและน้ำหนักลดในผู้ป่วยมะเร็งไตที่รักษาด้วยยาอินเตอเฟียรอน และควรทำการศึกษาเพิ่มเติมต่อไป

คำสำคัญ : อินเตอเฟียรอน, มีเจสทรอลอาซีเตท, อาการเบื่ออาหาร, น้ำหนักลด, เนื้องอกไต

นรินทร์ วรวุฒิ และคณะ
จดหมายเหตุทางแพทย์ ฯ 2000; 83: 123-128

* หน่วยอายุรศาสตร์มะเร็งวิทยา, ภาควิชาอายุรศาสตร์ และหน่วยรังสีวิทยา, ภาควิชารังสีวิทยา, คณะแพทยศาสตร์ จุฬาลงกรณ์-มหาวิทยาลัย, กรุงเทพ ฯ 10330