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Granulocyte-Macrophage Colony-Stimulating Factor, Interferon Alpha and Interleukin-2 as Adjuvant Treatment for High-Risk Renal Cell Carcinoma

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Abstract

This prospective, non-randomized study assessed toxicity and potential efficacy of low-dose granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon alpha (IFN) and interleukin 2 (IL-2) postoperatively in patients with high-risk renal cell carcinoma (RCC). Eligibility requirements were resected locally advanced (T3b-4 or N1–2) or metastatic (M1) RCC, no prior systemic therapy, and excellent organ function. Patients received treatment during 6 months: GM-CSF, 1 mcg/kg, 3 tiw, s.c., first week of each month; IFN, 10 MIU, 3 tiw, s.c., second week, and IL-2, 1 MIU, 3 tiw, i.v., third week. Fourth week of each month was free from treatment. The primary end-point was disease-free survival (DFS). Secondary end-points were progression rate, overall survival (OS), safety, and toxicity. Using the method of Dixon and Simon, the accrual goal was 35 patients. 35 patients were enrolled onto the study (28m/7f; median age = 46, range 21-71; ECOG 0-1; 14 (40%) pts with stage III and 21 (60%) pts with stage IV). Toxicity was minimal characterized by mainly flu-like syndrome and erythema in injection site. Median DFS was 14.1 months (95% CI, 3–20.2 months). At a median follow-up time of 5.1 years, progression rate was 65.7%, and OS was 40%. The median OS was 53.0 months (95% CI, 40.6–65.4 months). 5-years DFS and OS were similar between locally advanced and N2/M1 groups. Although the toxicities seen in this trial were low grade and regimen was well tolerated, low-dose GM-CSF, IFN and IL-2 did not improve DFS in comparison with historical control in patients with resected high-risk RCC.

Keywords: Renal cell carcinoma; High-risk; Adjuvant immunotherapy; GM-CSF; IFN; IL-2

Introduction

The estimated average 5-year survival rates in renal cell carcinoma (RCC) is 96% for patients presenting with stage I disease, 82% for stage II, 64% for stage III, and 23% for stage IV (DeVita and Rosenberg, 2008). After surgical excision, 20% to 30% of patients with localized tumors experience relapse. Lung metastasis is the most common site of distant recurrence, occurring in 50% to 60% of patients. The median time to relapse after surgery is 1 to 2 years, with most relapses occurring within 3 years. Longer disease-free intervals between diagnosis and recognition of metastatic disease are associated with longer projected survival. Adjuvant treatment after nephrectomy currently has no established role in patients who have undergone a complete resection of their tumor. No systemic therapy has been shown to reduce the likelihood of relapse. Randomized trials comparing adjuvant interferon alpha (IFN) or high-dose interleukin 2 (IL-2) with observation alone in patients who had locally advanced, completely resected RCC showed that no delay in time to relapse or improvement in survival was associated with adjuvant therapy (Clark et al., 2003; Messing et al., 2003; Trump et al., 1996). Observation remains standard care after nephrectomy, and eligible patients should be enrolled in clinical trials, if available. We hypothesized that granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN and IL-2 can stimulate large number of T-lymphocytes, antigen-presenting cells and can induct anti-tumor immunity in RCC patients. We therefore performed a prospective, non-randomized trial evaluating toxicity and efficacy of 6-months course of low-dose GM-CSF, IFN and IL-2 postoperatively in patients with high-risk RCC.

Materials and Methods

Patients

Patients were eligible for enrollment onto this trial if they were older than 18 years and had completely resected advanced high-risk RCC as defined by one of the following pathologic stages: T3b-c, T4, or N1–2, or M1 disease resected to no evidence of disease (AJCC-TNM, 2002). Patients must have recovered from any effects of surgery, which must have been performed within 10 weeks of enrollment. The patients had to meet the following eligibility criteria: an excellent performance status (Eastern Cooperative Oncology Group performance status of 0 or 1); adequate organ function defined as WBC count ≥ 4,000/μL, platelet count ≥ 100,000/μL, hemoglobin ≥ 10 g/dL, serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min, and direct bilirubin ≤ 1.5 mg/dL; and forced expiratory volume at 1 second more than 2.0 L or 75% of predicted for height and age from pre-enrollment pulmonary function testing. No history or evidence of cardiac disease on ECG was allowed. No prior systemic treatment for RCC was allowed, but patients may have received prior loco regional radiation therapy to solitary resectable metastases, which must have undergone surgical resection before enrollment. No prior history of invasive malignancy in the past 5 years or human immunodeficiency virus positivity was allowed; female patients were required to have a negative pregnancy test; and all patients were required to give written informed consent to participate. The institutional review boards for the protection of human subjects at each participating institution approved the study.

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Treatment and Follow-up

The planned treatment consisted of six cycles of immunotherapy during 6 months. One treatment cycle included 3 weeks of treatment and one week of rest. The GM-CSF was administered subcutaneously, 1 mcg/kg, 3 times per week, first week of each cycle. The IFN was administered subcutaneously, 10 MIU, 3 times per week, second week of each cycle. The IL-2 was in low-dose fashion: intravenously, 1 MIU, 3 times per week, third week of treatment cycle.

Standard supportive therapy was used to treat the typical immunotherapy–induced capillary leak syndrome, including low-dose vasopressor support, antipyretics, antinausea, and antidiarrheal medications (Fleischmann et al., 1997). All toxic effects were scored according to the National Cancer Institute Common Toxicity Criteria version 3.0.

Follow-up was identical for all patients: patients underwent evaluation with office visits, laboratory work-ups, and radiographic imaging (computed tomography scans of the chest, abdomen and pelvis, and bone scan) every 3 months for 2 years, then every 4 months for 1 year, then every 6 months during years 4 and 5, then yearly until recurrence or death. Documentation of recurrence was based on radiographic and clinical findings.

Statistical considerations

The primary end-point was disease-free survival (DFS). DFS was calculated from the day of registration on study to documented recurrence or death; patients remaining disease-free were censored at the date of last follow-up. In the recently closed CWG randomized trial, the median DFS for all patients enrolled was 28 months. Clark et al. (2003) using the method of Dixon and Simon (Galligioni et al., 1996), a sample size of 35 evaluable patients followed over 12 months will ensure at least 80% probability of detecting a minimum of 50% improvement in the median DFS compared to this CWG study at the 0.05 significance level (with a one-sided test).

Secondary end-points were progression rate, overall survival (OS), safety, and toxicity. OS was measured from the day of registration on study until death from any cause. The distributions of DFS and OS were estimated by the Kaplan-Meier method. All analyses were conducted in SPSS 17 (IBM Company).

Results

Thirty-five patients were entered on the study between May 2004 and June 2005. All patients could be evaluated for the protocol end points. Twenty-eight were men, and 7 were women. The median age of the population was 46 years (range, 21-71). Pretreatment patient and tumor characteristics are as follows: Eastern Cooperative Oncology Group performance status was 0 for 29 patients and 1 for 6 patients; 34 tumors (97%) were clear cell RCC and 1 tumor (3%) was sarcomatoid RCC; 12 patients (34%) had T3b (N0) or N1 (T1–3b) stages, 3 patients (9%) had T3c or T4 (N0–1), 20 patients (57%) had N2 (T1–4) or M1 resected to no evidence of disease. Disease in 21 (60%) patients was pathologic stage IV. The median follow-up time was 5.1 years for surviving patients.

The toxicity of the low-dose immunotherapy was as expected. There were no unexpected adverse events or treatment-related deaths as a result of this therapy (Table 1). The most common grade 1 toxicity was fever, which occurred in 91% of patients. Nine percent of the 35 patients treated with IL-2 experienced hypotension of grade 2 toxicity. There were neither serious hematological side effects no toxicity grade 3 or 4. All toxicities resolved after discontinuation of therapy. The range and median number of doses were similar for patients with locally advanced disease and those with resected metastases.

The median DFS was 14.1 months (95% CI, 3–20.2 months). It was therefore concluded by the review committee that there was no evidence to indicate that adjuvant therapy would have the projected 50% absolute increase in DFS over that of historical control (28 months). At the time of the first analysis (12 months), 16 of 35 (46%) patients had disease progression or death.

Toxicity	No.(%) of patients	GM-CSF		IFNα		IL-2	
		Toxicity grade	Rate (%)	Toxicity grade	Rate (%)	Toxicity grade	Rate (%)
Fever	32 (91.4)	1	5.7	1	43	1	17.1
				2	25.7		
Erythema in injection site	24 (68.6)	1	65.7	1	2.9	1	-
Hypotension	12 (34.3)	-	-	-	-	1	25.7
						2	8.6
Anorexia	9 (25.7)	-	-	1	17.1	1	8.6
Nausea	8 (22.9)	-	-	1	14.3	1	8.6
Lymphopenia	7 (20)	-	-	-	-	1	20
Fatigue	6 (17.6)	1	2.9	1	11.4	1	2.9
Allergy	3 (8.6)	1	8.6	-	-	-	-
Insomnia	3 (8.6)	-	-	1	5.7	1	2.9

Table 1: Adjuvant immunotherapy toxicities.

	Overall Sample (N = 35)	**Locally Advanced Only** (N = 15)	**N2/M1 Only** (N = 20)
Disease-free survival			
2-year, %	40	47	35
95% CI	30 to 50	41 to 53	29 to 44
3-years, %	40	47	35
95% CI	30 to 50	41 to 53	29 to 44
5-years, %	31	33	30
95% CI	27 to 35	23 to 42	28 to 37
Overall survival			
2-year, %	77	73	80
95% CI	68 to 100	63 to 100	74 to 100
3-years, %	66	60	70
95% CI	52 to 83	55 to 89	59 to 94
5-years, %	40	33	45
95% CI	25 to 54	21 to 45	22 to 56
Abbreviations: CI, confidence interval.			

Table 2: Disease-Free Survival and Overall Survival.

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At a median follow-up time of 5.1 years, progression rate was 65.7% (23 from 35 patients). First failure was local recurrence, regional lymph nodes, or both in 6 (26%) patients, distant in 14 (61%) patients, new primary in 1 (4%) patient, and death without disease progression in 2 (9%) patients. The lung and lymph nodes were the most common sites of recurrence (observed in 70% of patients with recurrent disease). After disease progression most patients were enrolled onto other clinical trials during which they received another form of systemic immunotherapy or targeted therapy. Three patients underwent surgical resection of recurrent disease.

The median OS was 53.0 months (95% CI, 40.6–65.4 months). 5-years DFS and OS were similar between locally advanced and N2/M1 groups (Table 2). As of the writing of the report, 16 patients remain alive and 12 patients have no disease progression; the longest recurrence-free time is 68 months.

Discussion

The concept of systemically treating patients at high risk of micrometastatic disease after surgical resection of the primary tumor has been explored in many different cancers, including breast, lung and colon. There are several reasons why the concept of adjuvant therapy in RCC has not been explored fully and prospectively, including the paucity of fully studied systemic treatments for RCC, the high toxicity profile of available agents, and that the incidence of RCC is not as high as that of other cancers, making accrual to large randomized trials difficult.

Tumor cells express tumor antigens that are present on the cell surface by MHC class I or class II molecules, and are capable of eliciting tumor-specific immune responses. These immune responses are mediated by CD8+ T lymphocytes and the responses may be further amplified by cytokines secreted by CD4+ helper cells, such as IL-2 and IFN. A rationale therefore exists to immunise patients against antigens derived from tumor cells, either alone or combined with hormones, cytokines or immune adjuvants, such as BCG to further enhance responses.

In a prospective randomized trial, 43 patients were randomly allocated to either adjuvant hormonal immunotherapy or hormonal therapy after nephrectomy. Immunotherapy consisted of autologous irradiated tumor cells admixed with BCG administered intradermally and endolymphatically. At a median follow-up of 30 months, although there was a trend for a longer DFS in patients with stages I-III RCC with localized disease, and longer survival in those with metastatic disease ($P < 0.07$), they were not statistically significant (Adler et al., 1987). Another prospective study of 120 patients randomized to either an untreated group or a group receiving autologous irradiated tumor cells mixed with BCG after radical nephrectomy for RCC (pT1–3b pN0 or pN+) was reported (Galligioni et al., 1996). At a median follow-up of 61 months, there was no statistically significant difference in either 5-year DFS (63% for treated and 72% for control patients) or 5-year overall survival (69% and 78%, respectively).

Three trials examined the effects of IFN as an adjuvant therapy after complete surgical resection, compared with observation (Lam et al., 2004). None of these trials showed a statistically significant improvement in endpoints such as the time to relapse or overall survival. A randomized phase III ECOG/Intergroup trial of adjuvant IFN after complete resection of locally extensive RCC (pT3–4a and/or pN+ disease) showed that adjuvant treatment did not contribute to survival or relapse-free survival in this group of patients (Messing et al., 2003). A multicentre, prospective, randomized, controlled phase III Cytokine Working Group trial assessed high-dose bolus IL-2 after surgery in patients with high-risk RCC, which included resected

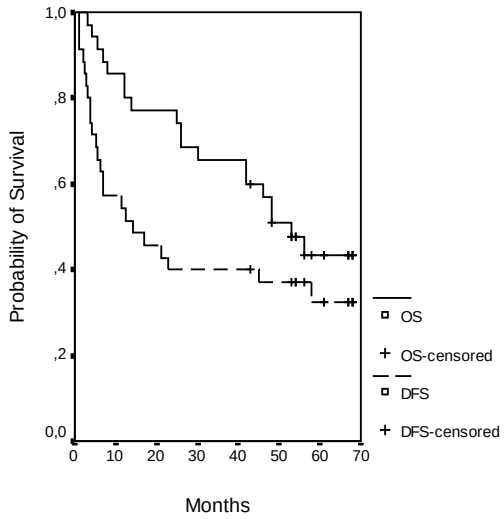

Figure 1: Overall and Disease-Free Survival.

locally advanced (T3b-4 or N1-3) or metastatic (M1) RCC and no previous systemic therapy. This study concluded that although one course of high-dose bolus interleukin-2 was feasible, there was no improvement in DFS over the observation group (Clark et al., 2003).

In our prospective study we evaluated toxicity and efficacy of low-dose GM-CSF, IFN and IL-2 postoperatively in patients with high-risk RCC. We suggested that three cytokine stimulate variety of immune cells, and induct anti-tumor immunity in RCC patients. High-risk RCC included T3b-c, T4, or N1–2, or M1 disease resected to no evidence of disease (AJCC-TNM, 2002). Although the toxicities seen in this trial were low grade and regimen was well tolerated, cytokines did not improve DFS in comparison with historical control. Most patients had disease progression within first 2 years after surgery. Disease-free survival and OS rates at 5 years were 31% and 40%, respectively (Figure 1).

References

1. Adler A, Gillon G, Lurie H, Shaham J, Loven D, et al. (1987) Active specific immunotherapy of renal cell carcinoma patients: a prospective randomized study of hormono-immuno versus hormonotherapy. Preliminary report of immunological and clinical aspects. J Biol Response Mod 6: 610-624.
2. Clark JI, Atkins MB, Urba WJ, Creech S, Figlin RA, et al. (2003) Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. J Clin Oncol 21: 3133-3140.
3. DeVita VT Jr HS, Rosenberg SA (2008) Cancer Principles and Practice of Oncology. 8th ed. Lippincott Williams & Wilkins, Philadelphia, PA.
4. Dixon DO, Simon R (1998) Sample Size Considerations for Studies Comparing Survival Curves Using Historical Controls. J Clin Epidemiol 41: 1209-1231.
5. Fleischmann J, Alyskewycz M, Flanigan RC (1997) Stage III renal cell carcinoma: Staging subcategories and prognosis. Presented at Am Urol Assoc Annual Meeting, New Orleans, LA.
6. Galligioni E, Quaia M, Merlo A, Carbone A, Spada A, et al. (1996) Adjuvant immunotherapy treatment of renal carcinoma patients with autologous tumor cells and bacillus Calmette-Guerin: five-year results of a prospective randomized study. Cancer 77: 2560-2566.
7. Lam JS, Belldegrun AS, Figlin RA (2004) Advances in immune-based therapies of renal cell carcinoma. Expert Rev Anticancer Ther 4: 1081-1096.
8. Messing EM, Manola J, Wilding G, Propert K, Fleischmann J, et al. (2003) Phase III study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: an Eastern Cooperative Oncology Group/Intergroup trial. J Clin Oncol 21: 1214-1222.
9. Trump DL, Elson P, Propert K, Pontes J, Crawford E, et al. (1996) Randomized, controlled trial of adjuvant therapy with lymphoblastoid interferon (L IFN) in resected, high risk renal cell carcinoma (HR-RCC). ASCO Annual Meeting Abstract 648.