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Review Article

SYSTEMIC THERAPY FOR RENAL CELL CARCINOMA

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ABSTRACT

Purpose: We review the status of systemic therapy for patients with advanced renal cell carcinoma.

Materials and Methods: A literature search was performed on MEDLINE and CANCERLIT to identify results of systemic therapy for patients with renal cell carcinoma published from January 1990 through December 1998. Treatment results of chemotherapy agents, immunotherapy, combination programs and adjuvant therapy were reviewed.

Results: No chemotherapy agent has produced response rates that justify its use as a single agent. Interferon-α and interleukin (IL)-2 demonstrated low response rates ranging from 10% to 20%. The results of 2 randomized trials suggest that treatment with interferon-α compared to vinblastine or medroxyprogesterone achieves a small improvement in survival. Response rates in patients treated with low dose IL-2 are similar to those achieved with a high dose bolus schedule but whether the responses are as durable is being addressed in an ongoing randomized trial. A randomized trial of interferon-α plus IL-2 compared to monotherapy with either agent showed increased toxicity but no improvement in survival. In 3 randomized trials no survival benefit was associated with adjuvant interferon-α therapy following complete resection of locally advanced renal cell carcinoma.

Conclusions: Despite extensive evaluation of many different treatment modalities, metastatic renal cell carcinoma remains highly resistant to systemic therapy. A few patients exhibit complete or partial responses to interferon and/or IL-2 but most do not respond, and there are few long-term survivors. Preclinical research, and clinical evaluation of new agents and treatment programs to identify improved antitumor activity against metastases remain the highest priorities in this refractory disease.

KEY WORDS: carcinoma, renal cell; drug therapy; interleukins; interferons

Estimates of annual new diagnoses of renal cell carcinoma have been increasing steadily.[1] Surgical resection of the primary tumor for patients with localized disease remains the mainstay of therapy. However, renal cell carcinoma is characterized by a lack of early warning signs, resulting in a high proportion of patients with metastases at diagnosis or relapse following nephrectomy. The outlook for patients with distant metastases is poor, with a 5-year survival rate of less than 10% for those presenting with stage IV disease.[1] Prior reviews have shown that renal cell carcinoma is resistant to chemotherapy.[2–5] Immunotherapy with interleukin (IL)-2 and/or interferon-α achieves responses in 10% to 20% of patients,[6,7] some of which are durable.[8] Management of advanced renal cell carcinoma remains a significant challenge to the clinician. We review the status of systemic therapy for renal cell carcinoma based on a review of the literature from 1990 through 1998.

EVALUATION OF THERAPY

Clinical trial methodology. Phases II and III clinical trials are the primary means of evaluating the efficacy of new agents and combinations. A phase II trial is designed to identify the activity of a drug or combination in a defined patient population with a particular tumor type. Dose and schedule are based on an earlier phase I trial. The intent is to assess efficacy and toxicity for patients with a specified malignancy, and thereby decide if further testing is worthwhile. A phase III trial is a randomized comparison between a new treatment program or agent and a standard care program. In the phase III trial the effect of treatment relative to the natural history of the disease, and whether a new treatment is more effective and/or less toxic than standard therapy are evaluated.

A phase II trial requires a clearly defined end point to evaluate efficacy accurately. For solid tumors disease must be measurable by physical examination or radiography so that response to the agent can be followed. The clinical response is determined to be complete, partial, stable disease or progression.[9] The primary end point for phase III trials is usually survival but may include response, progression or relapse-free survival and quality of life. The clinical methodology for evaluating an antitumor effect is determination of the proportion of patients who achieve a major response or response, defined as disappearance of all evidence of tumor (complete) or more than 50% decrease in tumor burden (par-

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sectional area for measurable tumors before and after (or during) treatment are compared.

Evaluation of treatment outcome for renal cell carcinoma. Several aspects of efficacy assessment are particularly relevant to clinical trials for renal cell carcinoma. Spontaneous regression must be considered when treatment results show low response activity. Metastatic renal cell carcinoma is characterized by variability in clinical course, and spontaneous regressions are well documented.[10] A phase II trial was performed on referral patients with metastatic renal cell carcinoma who were identified prospectively and treated with observation only until evidence of progression. Of 73 patients 5 (7%) had spontaneous complete or partial response and 12% remained progression-free for 12 months or more.[11] A randomized trial comparing interferon-γ to placebo in 197 patients with advanced renal cell carcinoma showed a 7% response rate in the placebo group, which was higher than that for the group treated with interferon-γ.[12] Therefore, tumor regression or prolonged stabilization of disease following treatment with an investigational agent must be considered in the context of the natural history of renal cell carcinoma.

The relative efficacy of a treatment program cannot be assessed by comparison of response rates from individually conducted phase II trials. Responses to high dose bolus IL-2 administration vary from 33%[13] to 0%[14] according to patient selection. Phase III randomized trials are required for definitive comparison of treatment programs. Also, the importance of independent response assessment was noted in a recent phase III trial comparing interferon-α, IL-2 and combination therapy.[15] Response assessment by a blinded peer review evaluation committee revealed major disagreements in 40% of patients achieving a major response as determined by the treating physician.[16] The authors concluded that the discrepancy was due to the increasing complexity of response assessment based on modern imaging techniques requiring collaboration between well trained clinicians and radiologists. They recommended updated guidelines of response assessment based on new imaging techniques and formal review of response by an independent evaluation committee for therapeutic trials.

Clinical trials for renal cell carcinoma may consider additional end points of treatment outcome, such as progression-free survival. Standard response criteria were based on assessment of cytotoxic agents. Patients showing response to immunotherapy with shrinkage of metastatic disease in the setting of a relatively stable bulky renal primary tumor may not meet standard criteria for partial response, due to the large bi-dimensional area of the tumor.[17] This factor may contribute to higher response rates associated with interferon-α and IL-2 treatment in phase II trials with a high proportion of nephrectomy cases. Also, immunotherapy and recent treatment strategies, such as angiogenesis inhibitors, could show an antitumor effect by producing prolonged stabilization of disease or slowing tumor regression during the course of many months. Therefore, time to progression and measurements of selected metastatic sites may be considered additional therapeutic end points of phase II clinical trials for renal cell carcinoma.

THERAPY FOR METASTATIC RENAL CELL CARCINOMA

Chemotherapy and resistance modulation. Studies continue to show that renal cell carcinoma is resistant to cytotoxic chemotherapy. From 1990 through October 1998, 33 chemotherapy agents were studied in 51 phase II trials comprising 1,347 patients (table 1).[18–68] The most extensively studied drugs were floxuridine and fluorouracil. In 1 trial a 20% response rate was reported with continuous intravenous larly response rates ranged from 0% to 14%.[37–39,41,69–71] A randomized multicenter trial of floxuridine administered by flat continuous infusion versus a circadian modified 14-day infusion schedule has been performed. The preliminary report on 82 patients demonstrated an overall 9% response rate.[72] Responses were generally short, lasting several months. To our knowledge there has been no benefit from the addition of fluorouracil modulators, such as calcium folinate. The low antitumor effect prompted the inclusion of floxuridine or fluorouracil, with interferon-α with or without IL-2. Results of phases I[73] and II[74] trials suggest synergy for fluorouracil with gemcitabine, and further study is warranted.

Several studies in the 1970s and early 1980s suggested that vinblastine had activity as a single agent against metastatic renal cell carcinoma.[4] This finding was the basis for including vinblastine as a part of combined therapy with interferon-α or more recently with agents that modulate multidrug resistance. Multidrug resistance was first recognized in the laboratory when models exposed to a single drug had broad cross-resistance to a group of distinct cytotoxic agents, and was associated with the MDR1 gene and its protein product, P-glycoprotein. Attempts to modulate multidrug resistance were judged particularly relevant to renal cell carcinoma since there is nearly uniform expression of P-glycoprotein on these cells. Multidrug resistance reversal agents were studied in 14 clinical trials for renal cell carcinoma in combination with vinblastine[75–85] or doxorubicin[86,87] (table 1). None was shown to enhance an antitumor effect. Moreover, the response rate to vinblastine alone or with a modulating agent in these more recent trials was 3% in 277 patients.[68,75,76,78–85] This lack of antitumor activity demonstrates that vinblastine is ineffective and emphasizes the need for new insight into overcoming drug resistance. The results of hormonal therapy have been equally disappointing (table 1).[88–91] In addition to single agents, combinations of chemotherapy plus hormonal agents have been studied but likewise are ineffective and result in additive toxicity. No chemotherapy or hormonal therapy has produced response rates that justify use as a single agent. The study of new agents is indicated in chemotherapy naive patients.

Immunotherapy. The 2 agents extensively studied in phase II trials in the 1980s that demonstrated low antitumor activity were interferon-α and IL-2.[1,6] Interferon-γ showed similar activity in phase II trials[6] but a randomized placebo controlled trial showed no difference in response or survival.[12] IL-12, which showed antitumor activity in phase I trials, was the most promising new agent studied in phase II trials.[88,92–106] The randomized phase II-III trial was stopped early due to a low response rate with IL-12 as a single agent.[107] Based on synergy with IL-2 in animal models,[108] study of this combination is warranted.

Interferon. Overall response to interferon-α in 1,042 patients was 12%.[6] Longer survival is associated with high performance status, prior nephrectomy and lung predominant metastases,[109,110] and a 30% response (complete plus partial) rate has been reported.[111] Average time from start of treatment to objective response is 3 to 4 months.[6] Response to interferon-α as well as other immunotherapies is characterized by slow regression of tumors, with patients meeting criteria for a partial response after as long as 12 months of therapy. Duration of response rarely has exceeded 2 years but long-term survivors following treatment with interferon-α have been reported.[109] A dose of 5 to 20 million units of recombinant interferon-α daily appears to have maximal efficacy and avoids the greater toxicity associated with higher doses.[112]

The potential role of interferon-α in prolonging survival compared to treatment with medroxyprogesterone or vinblastine has been evaluated in 4 randomized trials (table 2).

TABLE 1. *Results of phase II trials of new agents against renal cell carcinoma from 1990 to 1998*

	No. Evaluable	No. Complete + No. Partial Response (%)
Chemotherapy:		
Altretamine[18]	30	0
Amonafide[19, 20]	26, 17	0, 0
Caracemide[20]	17	0
Carboplatin[21]	18	0
13-cis-retinoic acid[22]	25	0
Cystemustine[23]	54	1 + 0 (2)
Dexniguldipine[24]	29	0 + 4 (14)
4′Deoxydoxorubicin[25]	15	0 + 1 (7)
Deoxycoformycin[26, 28]	19, 25	0, 0
Didemnin B[29]	21	0 + 1 (5)
Doxetaxel[30]	31	0 + 1 (3)
Echinomycin[31, 32]	47, 17	0 + 1 (2), 0
Edatrexate[33]	37	0 + 2 (11) (4)
5-Fluorouracil[34, 35]	35, 61	0 + 4, 1 + 2 (5)
Floxuridine circadian infusion[36–42]	56, 42, 14, 40, 26, 30, 50	4 + 7 (20), 3 + 3 (14), 0, 0 + 4 (10), 0 + 2 (8), 0 + 4 (14), 1 + 5 (11)
Fixed infusion[43, 44]	29, 15	1 + 5 (21), 0 + 2 (13)
Fotemustine[45]	16	0
Tegafur + uracil[46]	14	0
Gemcitabine[47, 48]	18, 37	0 + 1 (6), 1 + 2 (8)
Homoharringtonine[20]	14	0
Irinotecan[49]	17	0 + 2 (11)
Liposomal encapsulated doxorubicin[50]	14	0
Mafosfamide[51]	16	1 + 0 (6)
Menogaril[52, 53]	56, 15	0 + 3 (5), 0
Merbarone[54]	36	0 + 1 (3)
Navelbine[55, 56]	14, 24	0, 1 + 0 (4)
Paclitaxel[57]	18	0
Piroxantrone[58, 59]	32, 31	0, 0 + 1 (3)
Pyrazine[60]	15	0
Sulofenar (LY 186641)[61, 62]	18, 16	0, 1 + 0 (6)
Suramin[63, 64]	12, 26	0, 0 + 1 (4)
6-Thioguanine[65]	14	0
Topotecan[66]	14	0
Trimetrexate[67]	34	0 + 1 (4)
Chemotherapy + drug resistance modifiers:		
Vinblastine alone[68]	26	0 + 1 (4)
Vinblastine + acrivastine[75]	15	0
Vinblastine + dexverapamil[76–78]	12, 23, 18	0, 0, 0 + 1 (8)
Vinblastine + dipyridamole[79]	15	0
Vinblastine + cyclosporin[80]	16, 33	0, 0
Vinblastine + nifedipine[82]	14	0
Vinblastine + PSC 833[83]	29	2 + 1 (10)
Vinblastine + quinidine[84]	23	1 + 0 (4)
Vinblastine + tamoxifen[81]	35	1 + 0 (3)
Vinblastine + toremifene[85]	18	2 + 0 (11)
Doxorubicin + dexniguldipine[86]	20	0
Doxorubicin + [87]	11	0 + 1 (9)
Hormonal therapy:		
Tamoxifen[88–90]	25, 34, 59	2 + 1 (12), 1 + 3 (12), 0 + 1 (2)
Toremifene[91]	36	1 + 5 (17)
Immunotherapy:		
Cimetidine[92]	42	2 + 0 (5)
Granulocyte-macrophage colony-stimulating factor[93]	24	0
IL-1 β[94]	16	0
IL-4[95, 96]	18, 50	0, 0 + 1 (2)
IL-6[97, 98]	40, 12	0 + 2 (5), 0
IL-12[99, 100, 107]	20, 51, 30	0 + 1 (5), 1 + 0 (2), 0 + 2 (7)
Lanreotide[101]	30	0
Levamisole[102]	15	0
Linomide[103, 104]	63, 29	1 + 2, 0
Lonidamine[88]	19	1 + 1 (10)
Ranitidine[105]	16	1 + 2 (16)
Angiogenesis inhibitors:		
Razoxane[175]	31	0
TNP-470[176]	20	0 + 1 (5)

the other treatment arm.[113, 114] The 2 larger, more recent randomized trials had a small but significant ($p < 0.05$) improvement in survival with interferon-α therapy.[115, 116] In 1 study interferon-α resulted in improvement in median survival of 3 months compared to medroxyprogesterone.[115] In the other trial interferon-α plus vinblastine was compared to vinblastine alone, and the combination showed a benefit in median survival of 6 months.[116] The addition of vinblastine to interferon-α has been shown not to improve survival compared to interferon-α alone,[109–111] and several recent trials of vinblastine have failed to demonstrate single agent activity interferon-α. Although these 2 studies suggested a survival benefit, interferon-α therapy has resulted in a low response rate and rarity of long-term survival. Moreover, the impact of interferon on quality of life needs to be evaluated.

IL-2. In 3 randomized trials lymphokine activated killer cells did not add therapeutic benefit compared to IL-2 alone and could be omitted.[13, 117, 118] Food and Drug Administration approval for high dose bolus IL-2 was based on results of a multicenter series of 255 patients treated with high dose IL-2 alone. Complete plus partial responses were achieved in 14% of patients, some of whom had bulky metastases, and median

TABLE 2. *Randomized trials of interferon-α in patients with metastatic renal cell carcinoma*

References	No. Pts.	% Response	Median Survival (mos.)	Survival Benefit for Interferon (p value)
Steineck et al:[113]				
Interferon	30	6	7	No (not given)
Medroxyprogesterone	30	3	7	
Kriegmair et al:[114]				
Interferon + vinblastine	41	35	16	No (0.19)
Medroxyprogesterone	35	0	10	
Pyrhonen et al:[116]				
Interferon + vinblastine	79	16	17	Yes (0.0049)
Vinblastine	81	2	10	
Medical Research Council Collaborators:[115]				
Interferon	167	16	8.5	Yes (0.011)
Medroxyprogesterone	168	2	6	

duration of response of 54 months (range 3 to 107+).[8] These results were achieved in a group of patients who were young, had a high performance status and were treated at specialized centers.

Given the formidable toxicity and supportive care requirements associated with the high dose bolus regimen, lower doses of IL-2 have been studied. In a quantitative literature review of 39 published series of 1,291 patients response rates for inpatient high dose bolus, other inpatient dose or schedule and low dose outpatient schedules were 19%, 15% and 20%, respectively, with overlapping 95% confidence intervals.[117] The definition of low dose varies but 1 schedule consisted of a 5-day cycle administered subcutaneously every week for 6 consecutive weeks, with doses of 18 and 9 million units daily.[120] The relative efficacy of 3 schedules of IL-2 is being addressed in a randomized trial at the National Cancer Institute. Initially, this was a 2-arm study, and an interim report showed comparable efficacy and less toxicity associated with a low dose intravenous compared to a high dose bolus schedule.[121] A third arm of low dose subcutaneous IL-2 was added, and an update showed improved tolerability, and complete and partial responses in 11% of patients compared to 16% with high dose bolus therapy.[122] The major benefit cited for treatment with high dose bolus IL-2 in prior studies was durability of response,[123] and a comparison of durable responses awaits completion of trial accrual and long-term followup.[122] Prolonged response with high dose bolus IL-2 is noteworthy. The low response and 5-year survival rates, and formidable toxicity and supportive care requirements associated with this therapy emphasize the need to identify improved therapy through clinical studies.

Combination programs. Interferon-α plus vinblastine demonstrated a high response rate in several single arm phase II trials.[6] However, 3 randomized trials failed to show improved survival, and the addition of vinblastine to interferon contributed gastrointestinal and hematologic toxicity.[109–111] The combination of IL-2 and interferon-α was supported by preclinical studies showing synergistic actions. Many studied this combination, with wide variation in doses, schedules and routes of administration. Of 607 patients treated with IL-2 plus interferon-α in 23 clinical trials 19% responded, which was similar to that achieved with IL-2 alone.[124] The toxicities of these 2 agents in combination were additive, and the authors concluded that they provided no apparent benefit compared to IL-2 alone. A randomized phase II trial of high dose IL-2 with interferon-α versus high dose IL-2 alone showed no difference in response.[125] Moreover, in this randomized trial increased toxicity was seen with the addition of interferon-α to IL-2. Another randomized trial reported a higher response rate for the combination of IL-2 plus interferon-α compared to either agent alone.[15] However, no benefit in survival was associated with this combination compared to interferon or IL-2 monotherapy, and toxicity was out IL-2 has been given in various schedules as inpatient and outpatient therapy (table 3).[126–134] In several studies high response rates were reported for interferon, IL-2 and 5-fluorouracil.[126, 128, 135] However, others have shown a lower response rate for an identical or similar regimen, characterized by relatively short response and severe toxicity.[129–131, 134] The 3-drug 5-fluorouracil combination is being compared to interferon plus IL-2 in 2 randomized phase III trials under way in Europe. Preliminary results of 1 study showed no improvement in response for the combination of interferon and IL-2 plus 5-fluorouracil compared to interferon plus IL-2.[136] In this trial the response rate for the 3-drug regimen was 8%.[136] Inclusion of a fluoropyrimidine with interferon and IL-2 contributes to toxicity, and a conclusive statement on efficacy awaits further study in randomized trials.

Results of phase II trials suggested that retinoids augmented the antitumor effect of interferon-α against renal cell carcinoma.[17, 137–139] However, in a recently completed phase III trial no benefit was shown for the combination compared to interferon-α alone.[140] To our knowledge no sufficiently powered randomized phase III trial has demonstrated a survival benefit for combination therapy compared to single agent interferon or IL-2 (table 4).[15, 110, 111, 140–143] Each program showed promise in phase II trials, and reaffirms the necessity to conduct phase III trials to prove efficacy of novel treatment regimens.

Surgery. Nephrectomy is not indicated for inducing spontaneous tumor regression of distant metastases, based on the less than 1% incidence of this phenomenon, uncertain causality between primary tumor removal and spontaneous regression of metastases, and morbidity associated with nephrectomy in the setting of metastatic disease.[144] Nephrectomy in such a setting may be justified for select patients when the intent is to improve quality of life, such as the alleviation of local symptoms. Surgical resection of a solitary metastasis is performed in select patients, with a 5-year survival rate of approximately 30%.[145] In this respect patients with a solitary metastasis at initial diagnosis generally have an inferior outcome following resec-

TABLE 3. *Results of interferon-α, IL-2 and 5-fluorouracil combinations*

References	No. Evaluable	No. Complete + No. Partial Response (%)	Median Duration Response (mos.)
Kirchner et al[126]	246	26 + 54 (33)	Not stated
Hofmockel et al[127]	34	9 + 10 (38)	12
Ellerhorst et al[128]	52	4 + 12 (31)	17
Joffe et al[129]	38*	0 + 9 (24)	Not stated
Dutcher et al[130]	50	1 + 7 (16)	9
Gitlitz et al[131]	23	0 + 6 (26)	7+
Olencki et al[132]	18	0	Not stated
Tourani et al[133]	62	1 + 11 (19)	13+
Rayaud et al[134]	111	0 + 5 (2)	4

TABLE 4. *Phase III trial of combination programs against monotherapy with interferon-α or IL-2*

References	Treatment	No. Pts.
Fossa et al[110]	Interferon-α ± vinblastine	178
Neidhart et al[111]	Interferon-α ± vinblastine	165
Negrier et al[15]	Interferon-α + IL-2 vs. interferon vs. IL-2	425
Motzer et al[140]	Interferon-α ± retinoic acid	283
Sagaster et al[141]	Interferon-α ± coumarin + cimetidine	148
de Mulder et al[142]	Interferon-α ± interferon-γ	102
Figlin et al[143]	IL-2 ± tumor infiltrating lymphocyte	160

No survival benefit was noted for any combination therapy.

tion of the primary tumor plus metastasis compared to those who undergo resection of a solitary metastasis at relapse following nephrectomy.[145]

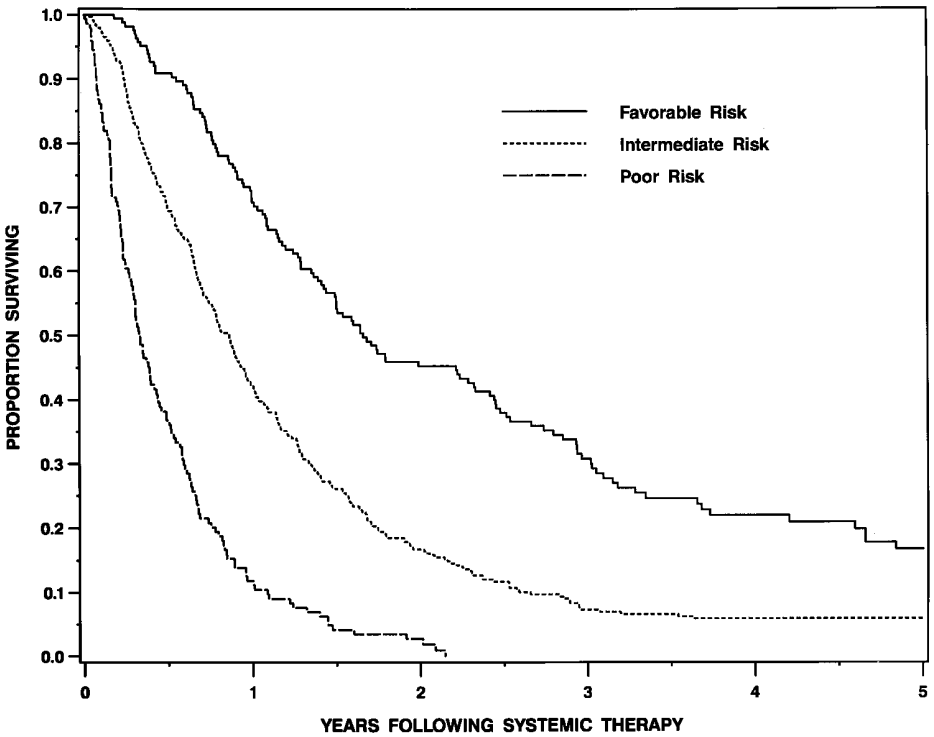
Prognostic factors for survival were evaluated in 278 patients who underwent surgical metastasectomy.[146] Favorable features for 5-year survival were a disease-free interval of greater than 12 versus less than 12 months (55% versus 9%), solitary versus multiple sites of metastases (overall survival 54% versus 29%) and age younger than 60 years (49% versus 35%). The 5-year survival was longer when the solitary site of resection was lung (54%) compared to brain (18%).

Controversy exists regarding nephrectomy to debulk tumor before treatment with immunotherapy. Theoretical advantages are reduction of a large, potentially immunosuppressive tumor burden and prevention of complications related to the primary tumor during systemic therapy. Disadvantages include the proportion of patients precluded from receiving systemic therapy because of rapid disease progression, perioperative complications and surgical mortality. The percentage of patients precluded from systemic therapy by cytoreductive nephrectomy ranges from 9% to 40%, and depends on selection by tumor size, performance status and co-morbid conditions.[147–153]

In 1 series of 28 patients treated during a 6-year period a 39% response to high dose IL-2 was reported after cytoreductive nephrectomy, with 26 (93%) eligible for systemic therapy postoperatively.[154] The largest series to our knowledge of 195 patients revealed that 121 (62%) were eligible for high dose IL-2 following cytoreductive nephrectomy, and the response rate of those treated with IL-2 was 18%.[152] Of the patients 40% who underwent nephrectomy did not ultimately receive immunotherapy because of complications from the procedure or clinical deterioration from progressive disease.

An alternative approach is to perform nephrectomy following immunotherapy on patients who have achieved a major response to assess pathological response and remove residual tumor.[151,155] Potential benefits include limiting the number of patients undergoing nephrectomy to those showing response and improved resectability of primary tumors.[151] Some have suggested that patients with a partial response at metastatic sites might benefit from aggressive surgical resection of residual metastatic disease.[156] The relative merit of initial versus delayed adjuvant nephrectomy for patients treated with immunotherapy needs to be further delineated. This issue is being addressed in a randomized phase III trial by the Southwest Oncology Group comparing interferon treatment with intact primary tumor versus nephrectomy followed by interferon therapy.

Prognostic factors. Determination of pretreatment features predictive of survival is valuable in directing therapy and interpreting results of clinical trials. Prognostic factors for patients with metastatic renal cell carcinoma vary but consistently include performance status, nephrectomy and a measure of extent of disease.[135,157–161] The relationship between pretreatment clinical features and survival was studied in 670 patients with advanced renal cell carcinoma treated in 24 Memorial Sloan-Kettering Cancer Center clinical trials of immunotherapy (interferon-α, IL-2) and chemotherapy between 1975 and 1996.[162] Median overall survival time was 10 months. Of the patients 57 (8%) remain alive with a median



Survival stratified according to risk group.[163] Risk factors associated with shorter survival were low Karnofsky performance status (less than 80%), high lactate dehydrogenase (greater than 1.5 times upper limit of normal), low hemoglobin (less than lower limit of normal), high

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