# Principles and Practice of Genitourinary Oncology


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# CHAPTER 85

# Chemotherapy for Renal Cell Carcinoma

Robert J. Motzer and Nicholas J. Vogelzang

Renal cell carcinoma (RCC) is a frequent cause of cancer mortality, responsible for more than 10,000 deaths per year in the United States.[1] This is the result of a lack of effective systemic treatment for patients with metastatic disease. Advanced RCC is characterized by a high level of resistance to all treatment modalities that have been studied, including cytotoxic agents, hormonal therapy, and biologic response modifiers. Although no single agent consistently shows a response proportion of 20% or higher, interleukin 2 (IL2) and interferon-$\alpha$ (IFNA) have demonstrated a low but reproducible response proportion in the 10% to 20% range, with durable responses of 5% or less.[2] The experience with chemotherapy and hormonal treatment are reviewed in this chapter, along with the general principles of management for patients with advanced RCC.

## CHEMOTHERAPY

Investigative efforts with chemotherapeutic agents have been extensive. Prior to 1975, nitrogen mustard,[3] hydroxyurea,[4] lomustine,[5] dacarbazine,[6] and hexamethylmelamine[6] were studied and did not show antitumor activity for RCC. A comprehensive review of the published literature shows that from 1975 through 1994, 80 single agents were studied in 155 trials (Table 85-1). Overall, 143 (4%) responses were achieved in 3951 evaluable patients. No agent has been shown to achieve major responses (complete or partial) in more than 20% of evaluable patients (with a sample size of 14 or more patients). Because of the lack of antitumor activity with conventional agents, the study of new agents remains justifiable in chemotherapy-naive patients.

The two agents that have been reported to have some, albeit minimal, antitumor activity are vinblastine and floxuridine (FUDR). Early studies suggested vinblastine had activity as a single agent, with a 26% response proportion reported in 135 patients.[7] This study served as the basis for the inclusion of vinblastine in trials as a part of combined therapy with IFN or with agents that modulate multidrug resistance (MDR). However, the results of more recent trials with vinblastine showed only nine responses in 135 (6%) evaluable patients (see Table 85-1).[74,90,195–199]

A 20% response proportion was reported with continuous intravenous infusion of FUDR administered according to a circadian schedule.[8] Response proportions ranged from 0% to 14% in seven subsequent trials of FUDR given in a similar fashion; one of these trials included folinic acid.[9–15] Enthusiasm prompted by the first trial resulted in the conduction of a randomized multicenter phase III trial of FUDR administered by flat continuous infusion versus a circadian modified 14-day infusion schedule. The preliminary report of this trial indicated that the response proportion for 82 evaluable patients treated in both arms was 9% (95% confidence interval, 4% to 17%).[16]

In addition to the trials of single agents, many combinations of chemotherapy agents have been studied.[17–25] These have not shown superior antitumor activity over the single agents, and toxicity was generally increased. The lack of antitumor activity for any of the many chemotherapy agents that have been studied emphasizes the need for novel treatment strategies in patients with advanced RCC.

## HORMONAL THERAPY

The rationale for the study of hormonal agents in RCC was provided by results obtained in animal models in the 1940s and the low concentrations of progesterone receptors found in human RCC.[26] The animal models showed hormone dependence and responsiveness in renal cancers induced in the Syrian hamster model.[26]

Bloom[26,27] initially reported a 16% to 21% response proportion for medroxyprogesterone (MP) in RCC. In the four trials published since 1980, the response proportion declined to 5% (Table 85-2).[28–31] Other hormonal agents also have been extensively studied. Testosterone and various other androgens achieved an overall 7% response proportion (see Table 85-2). The direct androgen antagonist flutamide was shown to be inactive.[32] The antiestrogens—tamoxifen, nafoxidine, and tormifene—were also studied in multiple trials and found to be relatively inactive, with a 6% response proportion achieved in 318 patients treated in 11 trials.

The addition of hormonal therapy to chemotherapy does not add efficacy; this was evident from the results of single-arm

**TABLE 85-1.** *Results of chemotherapy for renal cell carcinoma*

| Agent | Year and reference | No. of patients | Complete response/ partial response (%) |
|---|---|---|---|
| Acivicin | 1988[74] | 27 | 0/1 (4) |
| Aclacinomycin | 1984[75] | 15 | 0/0 (0) |
| L-Alanosine | 1988[74] | 36 | 1/0 (3) |
| 6-Aminonicatinamide | 1989[76] | 19 | 1/0 (5) |
| Ametantrone | 1985[77] | 25 | 0/2 (8) |
| Aminothiazide | 1988[74] | 46 | 0/1 (2) |
| Amonafide | 1991[78] | 24 | 0/0 (0) |
| Amsacrine | 1980[79] | 16 | 0/0 (0) |
| | 1980[80] | 21 | 0/0 (0) |
| | 1983[81] | 61 | 0/1 (2) |
| | 1983[82] | 42 | 0/1 (2) |
| 5′-Aza-2-deoxycytidine | 1987[83] | 12 | 0/0 (0) |
| Bisantrene | 1982[84] | 26 | 0/0 (0) |
| | 1982[85] | 37 | 0/2 (3) |
| | 1985[86] | 20 | 0/0 (0) |
| | 1985[87] | 14 | 0/0 (0) |
| | 1987[19] | 29 | 1/2 (10) |
| Bleomycin | 1975[88] | 15 | 0/0 (0) |
| | 1976[89] | 8 | 0/3 (37) |
| | 1977[90] | 7 | 0/0 (0) |
| Carboplatin | 1988[91] | 19 | 0/0 (0) |
| | 1990[92] | 18 | 0/0 (0) |
| Chlorozotocin | 1979[93] | 21 | 0/0 (0) |
| Cisplatin | 1978[94] | 23 | 0/0 (0) |
| | 1979[95] | 10 | 0/0 (0) |
| Cyclophosphamide | 1975[96] | 10 | 0/0 (0) |
| | 1979[97] | 44 | 0/2 (4) |
| | 1980[98] | 12 | 0/0 (0) |
| Plus misonidazole | 1986[99] | 30 | 0/1 (3) |
| Dactinomycin | 1981[23] | 61 | 0/1 (2) |
| 10-Deazaaminopterin | 1984[100] | 12 | 0/0 (0) |
| 2-Deoxycoformycin (Pentostatin) | 1991[101] | 18 | 0/0 (0) |
| | 1992[102] | 25 | 0/0 (0) |
| 4′-Deoxydoxorubicin (Esorubicin) | 1986[103] | 12 | 0/0 (0) |
| | 1986[104] | 27 | 0/0 (0) |
| | 1987[105] | 24 | 0/0 (0) |
| | 1989[106] | 19 | 1/1 (10) |
| | 1990[107] | 15 | 0/1 (7) |
| 4-Demethoxydaunorubicin | 1985[108] | 19 | 0/0 (0) |
| Dianhydrogalactitol | 1981[97] | 53 | 0/0 (0) |
| | 1982[109] | 41 | 0/1 (2) |
| Diaziquone | 1982[110] | 20 | 0/0 (0) |
| | 1984[111] | 29 | 0/0 (0) |
| | 1986[112] | 55 | 0/1 (2) |
| | 1986[113] | 15 | 0/0 (0) |
| Dibromodulcitol (Mitolactol) | 1981[114] | 13 | 0/1 (8) |
| | 1986[115] | 31 | 1/2 (10) |
| Didemnin B | 1990[116] | 21 | 0/1 (5) |
| | 1992[117] | 22 | 0/0 (0) |
| Docetaxel | 1994[118] | 18 | 0/0 (0) |
| Doxorubicin | 1977[119] | 38 | 0/2 (5) |
| Echinomycin | 1993[120] | 47 | 0/1 (2) |
| Elliptinium | 1985[121] | 8 | 0/0 (0) |
| | 1985[122] | 38 | 2/3 (13) |
| | 1988[123] | 14 | 0/0 (0) |
| 4'-Epi-adriamycin (Epirubicin) | 1982[124] | 20 | 0/0 (0) |
| | 1983[125] | 19 | 0/0 (0) |
| Estramustine | 1981[126] | 16 | 0/0 (0) |
| Etoposide | 1979[97] | 43 | 1/0 (2) |

**TABLE 85-1.** *Continued.*

| Agent | Year and reference | No. of patients | Complete response/ partial response (%) |
|---|---|---|---|
| Floxurine (circadian) | 1990[8] | 56 | 4/7 (20) |
| | 1990[9] | 42 | 3/3 (14) |
| | 1991[10] | 14 | 0/0 (0) |
| | 1991[11] | 40 | 0/4 (10) |
| | 1992[12] | 26 | 0/2 (8) |
| | 1993[13] | 28 | 0/4 (14) |
| | 1993[14] | 15 | 0/1 (7) |
| Plus folinic acid | 1991[15] | 15 | 0/0 (0) |
| By flat infusion | 1991[127] | 29 | 0/0 (0) |
| | 1993[128] | 29 | 1/5 (21) |
| Fludarabine | 1987[129] | 30 | 0/0 (0) |
| | 1989[130] | 15 | 0/0 (0) |
| 5-Fluorouracil | 1991[42] | 27 | 0/2 (7) |
| | 1993[43] | 35 | 0/4 (11) |
| | 1994[44] | 61 | 1/2 (5) |
| Plus folinic acid | 1989[45] | 14 | 0/0 (0) |
| Fosquidone | 1992[131] | 21 | 0/0 (0) |
| Fotemustine | 1991[132] | 62 | 1/3 (7) |
| | 1993[133] | 16 | 0/0 (0) |
| Ftorafur | 1993[134] | 14 | 0/0 (0) |
| Gallium nitrate | 1984[135] | 10 | 0/0 (0) |
| | 1987[136] | 25 | 0/1 (4) |
| Gemcitibine | 1992[137] | 30 | 1/2 (10) |
| | 1993[138] | 18 | 0/1 (6) |
| Hydroxyrea | 1981[139] | 19 | 0/1 (5) |
| ICRF-187 | 1986[140] | 40 | 0/0 (0) |
| Ifosfamide | 1980[141] | 11 | 0/1 (9) |
| | 1981[142] | 10 | 0/2 (20) |
| | 1987[143] | 16 | 0/0 (0) |
| | 1988[144] | 9 | 0/0 (0) |
| Liposomal encapsulated doxorubicin | 1995[145] | 14 | 0/0 (0) |
| Lomustine | 1977[90] | 9 | 0/0 (0) |
| | 1986[146] | 5 | 0/0 (0) |
| Lonidamine | 1986[147] | 25 | 0/2 (8) |
| | 1991[148] | 19 | 1/1 (10) |
| LY186641 | 1993[149] | 16 | 1/0 (6) |
| Mafosfamide | 1992[150] | 16 | 1/0 (6) |
| Melphalan | 1993[151] | 8 | 0/0 (0) |
| Menogaril | 1990[152] | 56 | 0/3 (5) |
| | 1991[153] | 15 | 0/0 (0) |
| Methodichlorophen | 1979[154] | 10 | 0/3 (30) |
| Methotrexate | 1980[20] | 8 | 0/2 (25) |
| Mitoguazone (methyl-GAG) | 1981[155] | 25 | 1/3 (16) |
| | 1981[156] | 31 | 0/0 (0) |
| | 1982[157] | 30 | 0/3 (10) |
| | 1981[158] | 14 | 0/0 (0) |
| | 1983[159] | 87 | 1/3 (4) |
| Mitomycin | 1987[160] | 12 | 0/3 (25) |
| Mitotane | 1981[161] | 12 | 0/0 (0) |
| Mitoxantrone | 1984[162] | 20 | 0/0 (0) |
| | 1984[163] | 49 | 0/0 (0) |
| | 1984[164] | 29 | 0/0 (0) |
| | 1986[165] | 48 | 0/0 (0) |
| Mitozolomide | 1989[166] | 17 | 0/0 (0) |
| N-methylformamide | 1986[167] | 16 | 0/0 (0) |
| | 1989[168] | 14 | 0/0 (0) |
| Navelbine | 1991[169] | 14 | 0/0 (0) |
| | 1993[170] | 24 | 1/0 (4) |

*(continued)*

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