

Chemotherapy of Metastatic Renal Adenocarcinoma with a Five-Drug Regimen*

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In the past, chemotherapy of renal adenocarcinoma has been relatively unsuccessful. The progestational agent, medroxy progesterone acetate (MPA), has been the most effective single agent, even though the response rate probably does not exceed 12%. This report describes the results of a program of combination therapy with MPA, cyclophosphamide, hydroxyurea, vinblastine and prednisone that was used on 42 patients, ten of whom had received prior MPA therapy. One complete remission and seven partial remissions were observed, only one of whom had received prior MPA therapy. Treatment of metastatic renal adenocarcinoma with combination chemotherapy should probably include MPA and adriamycin. The role of estrogen receptor (ER) and progesterone receptor (PR) as predictions of response to hormonal therapy in this disease looks encouraging, but the results reported to date have been limited.

Renal adenocarcinoma is one of the malignancies most resistant to control with systemic chemotherapy. Bloom and Wallace¹ in 1964 were the first to report that progestational steroids and androgenic steroids have a definite palliative effect in metastatic renal carcinoma. This treatment was based on experimental evidence of Bloom et al² who used androgens and progestins to block estrogen-induced renal carcinoma in hamsters. Our initial experience with these hormonal agents at Henry Ford Hospital was first reported in 1969³ and subsequently updated in 1973.⁴ Of the several chemotherapeutic agents we tested, only vinblastine had any effect, as noted in two of 15 patients. However, a summary of the literature before 1972 suggested that an approximate 20% response rate has been reported with cyclophosphamide, hydroxyurea and vinblastine.⁴ Since then, only the nitrosourea, CCNU, has seemed efficacious⁵ in treating renal carcinoma. Other studies have not been as encouraging.⁶

Many of the newer chemotherapeutic agents, including adriamycin,⁷ cis platinum,⁸ and chlorozotocin,⁹ have had trials as single drugs in metastatic renal adenocarcinoma, but no significant responses have been reported.

A variety of programs of combination chemotherapy have been reported, and a limited review of some are as follows:

- 1) MPA, BCG, adriamycin and vincristine (10/31)¹⁰
- 2) Methylprednisolone, CCNU, bleomycin (1/16)¹¹
- 3) Methylprednisolone, CCNU, bleomycin and adriamycin (3/14)¹¹
- 4) MPA, adriamycin, hydroxyurea and vinblastine (4/8)¹²
- 5) Testosterone, MPA, vincristine, actinomycin D and cyclophosphamide (0/4)¹³

It is apparent from this that adriamycin and MPA are among the more active of these combinations. Recent studies in passive and active immunotherapy are in progress, but it is too early to include their results in this partial review. The progestational steroid, medroxyprogesterone acetate (MPA),

Submitted for publication: June 18, 1979
Accepted for publication: August 1, 1979

* Supported in part by the Henry Ford Hospital Cancer Research Memorial Fund R10731; presented in part to the Michigan Urological Society, March, 1978

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has had extensive trials, and no significant toxicity is associated with its use. However, the response rate probably does not exceed 12%. Studies of estrogen receptor (ER) and progesterone receptor (PR) of kidney carcinoma suggest that the response rates to hormonal therapy in patients with positive ER and PR are higher than in patients with negative receptors. Of the five complete responses reported by our institution,^{3,4} three are still alive without evident disease and one died of unrelated causes. All of the surviving patients have had a 10+ year survival. Only one of the patients classified as a complete response to MPA has had a recurrence. All who experienced a partial or complete response had undergone a nephrectomy either at, or prior to, the time metastatic disease was diagnosed.

Methods

This report reviews our experience with a program of combination therapy consisting of MPA, vinblastine, cyclophosphamide, hydroxyurea and prednisone. The dosage schema is given in Table I. Forty-two patients were entered on the study. Ten had received prior progestational and/or androgenic therapy. Patients were entered on the study only if they had a predicted survival of at least eight weeks. All patients received at least two courses and were followed for a minimum of eight weeks.

Responses were evaluated as follows:

1. Patients were classified as complete responses if all evidence of measurable disease cleared for at least three months.
2. A partial response was declared if there was a 50% or more decrease in the diameters of all measurable lesions.
3. Either no change or a stable disease classification was used if the response was less than partial or the lesions did not appear to change for six months or longer.
4. A failure was defined if any new lesions developed or if there was an increase in the size of preexisting lesions by 25% or more.

TABLE I
Combination Chemotherapy Schema

| Drug | Dosage |
|-----------------------------|---|
| Cyclophosphamide | 400 mg / M ² day 1 IV |
| Vinblastine | 3 mg / M ² days 1 and 2 IV |
| Hydroxyurea | 500 mg / M ² days 8 to 28 orally |
| Medroxyprogesterone acetate | 1,000 mg q-wk IM x 4 wks, then 400 mg / wk |
| Prednisone | 50 mg / M ² po. q-d |

Results

As recorded in Table II, the combination program has produced only one complete response and seven partial responses. These responses are disappointing in that the response rate is not better than that observed with MPA therapy alone when all 42 patients are included. Of the patients who had received prior MPA treatment, only one of ten, or 10%, responded to this combination program. This patient had had a partial response to MPA therapy, whereas none of the others had responded to MPA therapy at all. However, in seven of 32 patients (21.8%) who had not received prior MPA, there was one complete response and six partial responses. This may be considered some improvement over MPA therapy alone; however, the difference is not significant by the X² method of analysis (p>0.05). The comparison with historical MPA controls as previously reported.⁴ The significance of the stable disease category (Table II) is difficult to interpret because of the variable nature of the disease. However, the survival statistics for these patients are definitely better than those for patients classified as failures to therapy. The one patient who responded completely is alive and has no measurable disease 42 months after therapy began. The median survival of the seven patients classified as partial responses is 18 months. Partial responses have been observed primarily in lung and subcutaneous metastases. However, in one patient with lytic osseous metastases to the skull healing of these lesions has been observed after ten months of therapy. In patients with stable disease, three had osseous metastases and four had only soft-tissue metastases. The current study employing five agents (MPA, vinblastine, cyclophosphamide, hydroxyurea and prednisone) did not show a significant improvement in response over MPA alone. For patients in the no change or stable category, median survival was 12 months; for those who failed to respond to therapy, median survival was 5 months.

TABLE II
Response to Combination Chemotherapy

| Patients (42) | Complete | Partial | Stable | Failure | Total |
|----------------------------|----------|---------|--------|---------|-------|
| Prior MPA Therapy (10) | 0 | 1 | | 9 | 10 |
| No Prior MPA Therapy (32) | 1 | 6 | 7 | 18 | 32 |
| Combination Program Totals | 1 | 7 | 7 | 27 | 42 |

Discussion

Metastatic adenocarcinoma of the kidney is a slowly progressive, relentless disease. Attempts to halt its course with combination chemotherapy have not met with great suc-

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cess, and progestational agent therapy continues to be the mainstay of any program. If possible, removal of the primary renal neoplasm appears to be important in effecting any control over the metastases.^{4,15} Other combinations of chemotherapeutic agents have been attempted, and some of these are reviewed. Apparently, including MPA and adriamycin in any combination may improve the response rate.

Conclusion

We recommend further exploration of other combinations of drugs which at this time should include MPA and

adriamycin. The use of MPA for patients with a high risk of recurrence should be considered as adjuvant to nephrectomy in cases of renal adenocarcinoma, especially in those patients with extension through the renal capsule or extension into the renal vein. Further evaluation of ER and PR is necessary to determine if these studies will be predictive of hormonal response.

Acknowledgments

The authors wish to thank Ms. Dorothy Gurwitz for help in preparing the manuscript.

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