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[Intervention Review]

Immunotherapy for advanced renal cell cancer

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ABSTRACT

Background

The course of advanced renal cell carcinoma is extremely variable, ranging from spontaneous remission to disease progression refractory to chemotherapy. Immunotherapy has held promise of improved outcomes based on uncontrolled studies and randomized controlled trials generally limited by small size and low power.

Objectives

To evaluate immunotherapy for advanced renal cell carcinoma by comparing: (1) high dose interleukin-2 to other options and (2) interferon-alfa to other options. The primary outcome of interest was overall survival at one year, with remission as the main secondary outcome of interest.

Search methods

A systematic search of the CENTRAL, MEDLINE, and EMBASE databases was conducted for the period 1966 through end of 2005. Handsearches were made of the proceedings of the periodic meetings of the American Urologic Association, the American Society of Clinical Oncology, ECCO - the European Cancer Conference, and the European Society of Medical Oncology for the period 1995 to 2005.

Selection criteria

Randomized controlled trials that selected (or stratified) patients with advanced renal cell carcinoma, utilized an immunotherapeutic agent in at least one study arm, and reported remission or survival by allocation. Fifty-eight identified studies involving 6880 patients were eligible and all but one reported remission; thirty-seven of these studies reported the one-year survival outcome.

Data collection and analysis

Two reviewers independently abstracted each article by following a prospectively designed protocol. Dichotomous outcomes for treatment remission (partial plus complete) and for deaths at one year were used for the main comparisons. Survival hazard ratios were also used for studies of interferon-alfa versus controls.

Main results

Combined data for a variety of immunotherapies gave an overall chance of partial or complete remission of only 12.4%, compared to 2.4% in non-immunotherapy control arms. Twenty-eight percent of these remissions were designated as complete (data from 51 studies). Median survival averaged 13 months (range by arm, 6 to 28 months). The difference in remission rate between arms was poorly correlated with the difference in median survival so that remission rate is not a good surrogate or intermediate outcome for survival for advanced renal cancer. We were unable to identify any published randomized study of high-dose interleukin-2 versus a non-immunotherapy control, or of high-dose interleukin-2 versus interferon-alfa reporting survival. High dose interleukin-2 did not give better overall survival compared to

the same therapy at one tenth the dose or to subcutaneous cytokine therapy, but may improve survival in the patients with bad prognostic factors based on subset analysis. Results from four studies (644 patients) suggest that interferon-alfa is superior to controls (OR for death at one year = 0.56, 95% CI 0.40 to 0.77). Using the method of Parmar 1998*, the pooled overall HR for death was 0.74 (95% CI 0.63 to 0.88). Of concern, a recent study currently available as a meeting report did not find a benefit to interferon-alfa in patients with advanced renal cell cancer of intermediate prognosis. The optimal dose and duration of interferon-alfa remains to be elucidated. The addition of a variety of enhancers, including lower dose intravenous or subcutaneous interleukin-2, has failed to improve survival compared to interferon-alfa alone. Two randomized studies have examined the role of initial nephrectomy prior to interferon-alfa therapy in highly selected fit patients with metastases at diagnosis and minimal symptoms; despite minimal improvement in the chance of remission, both studies of up-front nephrectomy improved median survival over interferon-alfa alone in this selected population.

Authors' conclusions

Interferon-alfa provides a modest survival benefit compared to other commonly used treatments. In fit patients with metastases at diagnosis and minimal symptoms, nephrectomy followed by interferon-alfa gives the best survival strategy for fully validated therapies. The need for more effective specific therapy for this condition is apparent.

PLAIN LANGUAGE SUMMARY

Immunotherapy for advanced kidney cancer

Cancer originating in the kidney in adults, known as renal cell carcinoma, is an important health problem (childhood Wilms' tumour is a different condition not covered in this review). The condition is rarely curable if it has spread to other organs at the time of diagnosis, if spread appears after initial removal of the affected kidney, or the kidney tumour is too extensive for surgery. Kidney cancer is resistant to conventional chemotherapy. The observation that these tumours can occasionally shrink without therapy, especially when spread to the lungs, suggested that drugs that work through the patient's immune system might be a useful approach. Because the course of kidney cancer is very variable between patients, studies were only included if patients consented to be randomly allocated to have the immunotherapy of interest or a control therapy. Any type of immunotherapy was accepted for inclusion in this survey.

A systematic search of reports published between 1966 and 2005 identified 58 different studies of immunotherapy in 6880 patients with advanced renal cell cancer. Thirty-seven studies reported the main outcome of interest, the chance of surviving for one year for each treatment tested. One study provides useful information about the effect of placebo, with 6% of patients having a partial remission and 25% having stable disease for more than six months. Other studies used hormone pills as control therapy, probably inactive agents. Of the many types of immunotherapy that have been tested, only interferon-alfa has been shown to improve the chance of surviving for one year. Interferon-alfa is normally made by white blood cells in response to viral infections. Originally obtained from human blood in tiny impure amounts, interferon-alfa can now be made as a pure product and is given by injection under the skin, usually three times per week. Four studies tested interferon-alfa in 644 patients with advanced kidney cancer and, compared to control therapy, this agent reduced the risk of death at one year by 46% and risk of death over the course of two years by 36%. The treatment has a low chance of shrinking cancers with partial remission seen in only 12.5% of patients. These studies included a representative sample of patients as long as they were ambulatory and without spread to the brain. Interferon-alfa therapy is very safe but causes an unpleasant flu-like syndrome of variable severity that tends to improve as treatment continues, with fatigue and loss of appetite.

Attempts to enhance the benefit of interferon-alfa by adding other drugs have been unsuccessful with the possible exception of adding cis-retinoic acid, related to Vitamin A, and this approach resulted in worse quality-of-life than interferon-alfa alone. However, in patients whose kidney cancer has visibly spread at the time of diagnosis, removing the kidney before giving interferon-alfa prolonged average survival by six months (two studies, combined data), the most impressive effect of any treatment for advanced kidney cancer so far demonstrated including the new targeted agents (see separate review). It has been suggested that the removal of the primary kidney tumour works by unblocking the patient's immune system but it is unknown if this procedure can be counted as an immune approach.

One goal of this review was to assess the benefit of high dose interleukin-2, an expensive and toxic treatment that was the only approved therapy for advanced kidney cancer in the United States at the time of the most recent review update in 2006. No studies of high dose interleukin-2 compared to a non-immunotherapy control were identified. High dose interleukin-2 gives equivalent survival to low dose interleukin-2 plus interferon-alfa, a combination known to have greater toxicity than interferon-alfa alone.

The main limitation of the studies surveyed in this review was their small size with consequent limited ability to demonstrate differences in efficacy between treatments tested. For example, three studies tested different doses of interferon-alfa but are too small to provide useful information on this point and consequently the optimal dose of this agent is unknown.