Drugs of the Future 2006, 31(6): 527-530
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CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.06.1000710

Minireview

Metastatic renal cell carcinoma: improving cytokine treatment with combination therapy

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CONTENTS

Abstract

Metastatic renal cell carcinoma (mRCC) is currently one of the most treatment-resistant malignancies. Immunotherapy with interferon alfa (IFN-α) or interleukin-2 (IL-2) is the standard of care for patients with advanced RCC. However, the overall response rate is very low and the prognosis of mRCC is currently extremely poor. Inspired by the promising results obtained from studies of lung and colon cancer, a number of studies evaluating combinations of traditional immunotherapy with other types of antitumor agents in the treatment of advanced RCC have recently been performed and promising results were reported.

Introduction

Renal cell carcinoma (RCC) is the most common type of kidney cancer. It accounts for about 3% of adult malignancies and is the tenth leading cause of cancer-related death in men. About 33% of patients with RCC have or will develop metastatic lesions during the course of the disease. Metastatic renal cell carcinoma (mRCC) is currently one of the most treatment-resistant malignancies (1, 2).

Clear cell carcinoma is the most common form of renal tumor. It accounts for 70-80% of all cases of RCC. Since the most common clear cell type of RCC is an immunogenic tumor, the main systemic treatment of mRCC has focused on immunotherapy. Interferon alfa (IFN-α) belongs to a family of cytokines with antiproliferative and immunomodulatory activity. Immunotherapy with IFN-α or interleukin-2 (IL-2) is currently the standard of care for mRCC. However, the objective response rates are very low (10-15%), and the overall prognosis of the disease is extremely poor, with a median survival of about 10 months (1, 2).

Compared to standard treatment alone, the addition of certain novel agents to conventional treatment has shown promising results in other types of cancer, such as lung and colon cancer. To determine whether combination therapy with IL-2 or IFN-α and other agents could improve efficacy in the treatment of advanced RCC, a number of clinical studies were recently performed, and more studies are currently under way.

Combination therapy with IL-2

WX-G250 with IL-2

Carbonic anhydrase $IX^{G250/MN}$ is present in over 95% of clear cell RCCs. WX-G250 (Wilex) is a chimeric monoclonal antibody that binds to carbonic anhydrase $IX^{G250/MN}$. Clinical studies of radiolabeled WX-G250 revealed excellent targeting to tumor lesions. Previous studies of WX-G250 in patients with mRCC suggested that WX-G250 itself might have antitumor activity.

To determine whether the addition of WX-G250 could improve the efficacy of low-dose IL-2 in the treatment of advanced RCC, a clinical study was carried out in 35 patients with progressive clear cell RCC. The patients received weekly infusions of WX-G250 for 11 weeks combined with a daily low-dose IL-2 regimen. A durable clinical benefit was achieved in 23% of patients. The mean survival time (22 months) was longer than with WX-G250 therapy alone (16 months). The treatment was well tolerated, with little toxicity (3).

Denileukin diftitox with IL-2

It has been suggested that denileukin diftitox (Ontak®; Ligand) may be able to carry IL-2 directly to the kidney so that IL-2 can stimulate white blood cells to kill cancer cells. It is therefore expected that addition of denileukin diftitox may be able to increase the efficacy of IL-2 in the treatment of advanced RCC. To determine the toxic effects and overall response rate of the combination of denileukin diftitox and high-dose IL-2 in patients with RCC, a randomized pilot study is currently being carried out in patients with mRCC (4).

Histamine dihydrochloride with IL-2

Since many types of cancer in adults arise in the setting of chronic inflammation, it has been suggested that the addition of histamine dihydrochloride (HDC, Ceplene™; Maxim), an inhibitor of the formation and release of phagocyte-derived reactive oxygen species (ROS), may improve the efficacy of IL-2 in the treatment of mRCC. To study the potential efficacy of histamine when used as combination therapy with IL-2 in the treatment of mRCC, two randomized phase II trials with and without HDC were carried out in parallel, one in Denmark and the other in the U.K. Patients receiving at least 80% of the scheduled drug doses within the first treatment course were included in the final analysis (5, 6). The study in Denmark showed that, by blocking the formation of phagocyte-generated ROS, histamine was able to enhance the effect of IL-2 in inducing natural killer (NK) and T-cells against oxidative damage, and combination therapy increased survival. However, the IL-2/HDC combination did not show better results than IL-2 alone in the study carried out in the U.K. The exact reasons why the two similar studies provided different results are not clear and further studies in larger number of patients are needed.

Bevacizumab with IL-2

A phase I study showed that the recombinant humanized monoclonal antibody bevacizumab (Avastin™; Genentech) could be safely administered alone or with traditional chemotherapy. A phase II study in patients with advanced RCC demonstrated that a high dose of bevacizumab significantly prolonged time to disease progression. A phase II trial of IFN-α with or without bevacizumab as first-line therapy for advanced RCC is currently under way (7).

Genistein with IL-2

It has been suggested that genistein may be able to interrupt the growth of cancer cells by blocking certain enzymes needed for cell growth and by blocking blood flow to the tumor. It is therefore expected that the combination of genistein and IL-2 may be associated with greater tumor cell kill.

To study the efficacy, side effect profile and effect on time to progression, a pilot phase II study of this combination in the treatment of mRCC is currently under way. The patients are given high-dose IL-2 over 15 min twice daily on days 1 and 15 and 3 times daily between days 2 and 5, as well as between days 16 and 19. Genistein is given twice daily on days 10-19. Results are pending (8).

IFN-α with IL-2

Recently, a clinical study of combined immunotherapy with low-dose IL-2 and IFN-α was performed in Japanese patients with mRCC who had previously undergone radical nephrectomy. The patients received an s.c. injection of IFN-α of 6 x 10^6 IU/day 3 times per week and an i.v. injection of IL-2 of 1.4 x 10^6 IU/day twice a week. Among the 13 treated patients, 1 dropped out because of severe side effects. Six of the 12 evaluable patients achieved objective responses and only 2 patients demonstrated progressive disease. The median duration of response in the 6 responders was 13.5 months. The main toxicity associated with the combination therapy was limited to WHO grade 1 or 2. The results showed that combined immunotherapy with IFN-α and IL-2 has good activity and safety in the treatment of mRCC. Because the number of patients enrolled in the study was rather small and the patients had undergone surgery to remove the tumor before therapy, a further study including a larger number of patients with a longer observation period is needed to confirm the high response rate of the combination therapy observed in this study (9).

Combination therapy with IFN-α

Sunitinib with IFN-α

A randomized phase III trial, sponsored by Pfizer, is currently under way to study the efficacy and safety of sunitinib malate (Sutent®) alone or in combination with IFN-α as first-line therapy for mRCC (10).

Sorafenib with IFN-α

Like genistein, sorafenib (Nexavar®; Bayer, Onyx) may be able to interrupt the growth of tumor cells by blocking certain enzymes needed for cell growth and by blocking blood flow to the tumor. With the aim of killing more tumor cells using sorafenib and IFN-α together, a randomized phase II study of sorafenib with or without low-dose IFN-α is in progress in patients with mRCC, and results are pending (11).

Isotretinoin with IFN-α

To determine whether combination therapy with isotretinoin (13-*cis*-retinoic acid) plus IFN-α is superior to IFN-α alone in the treatment of mRCC, a randomized phase II/III trial was conducted in 320 patients with advanced RCC. Subcutaneous IFN-α was given to patients daily starting at a dose of 3 million units (MU), which was escalated every 7 days from 3 to 9 MU in increments of 3 MU. Patients randomly assigned to the combination therapy were given isotretinoin 1 mg/kg/day plus IFN-α. The median time to progression was 5.1 months for the patients treated with the combination and 3.4 months for those treated with IFN-α alone. Progression-free survival rates at 6 months were 43% for patients on the combination and 30% for those given IFN-α alone, and the corresponding survival rates at 12 months were 27% and 17%. The median overall survival was 17.3 and 13.2 months, respectively, for the combination and IFN-α alone. However, the improved efficacy of the combined therapy was associated with increased tox-

icity; 22% of the patients given the combination stopped treatment due to toxicity compared with 16% of the patients treated with IFN-α alone (12).

Thalidomide with IFN-α

It has been suggested that thalidomide may be able to inhibit the growth of tumor cells by blocking blood flow to the tumor. To determine whether combination with thalidomide can increase the efficacy of IFN-α in the treatment of mRCC, a randomized phase II study of IFN-α with or without thalidomide is currently being performed in patients with mRCC (13, 14).

Temsirolimus with IFN-α

In a phase II study of temsirolimus (CCI-779; Wyeth) in the treatment of advanced RCC, 7% of the patients achieved an objective response, with a median time to tumor progression of 5.8 months and a median survival of 15 months (15). To compare the efficacy of combination therapy with temsirolimus + IFN-α and temsirolimus and IFN-α alone as first-line therapy, a phase III study has been completed in patients with RCC (1, 2, 16). Preliminary data from an interim analysis showed no significant difference in survival between IFN-α and IFN-α + temsirolimus (7.3 months *vs*. 8.4 months), while temsirolimus alone significantly increased overall survival (10.9 months) (17).

Other studies

Significant advances in the understanding of the molecular mechanisms of RCC have led to the identification of potential targets and the rational design of promising therapies. Many of the agents target the pathways that involve signal transduction and angiogenesis. The involvement of the Von Hippel-Lindau (VHL) protein pathway in clear cell RCC suggests that downstream targets of this pathway, including vascular endothelial growth factor (VEGF) in endothelial cells, platelet-derived growth factor (PDGF) in endothelial cells and pericytes, and epidermal growth factor receptor (EGFR) in tumor cells, are all potential therapeutic targets. Studies of the efficacy and safety of these agents alone in the treatment of RCC, as well as other types of cancers, are under way. Interesting results have been reported. Agents targeting VEGF include bevacizumab. Agents targeting the VEGF receptor (VEGFR) include vatalanib, sunitinib and sorafenib. Agents targeting the EGFR include gefitinib, cetuximab, erlotinib and panitumumab (1, 2).

Because the Ras/MEK/ERK pathway is an important downstream converging point for signaling through the VEGFR, PDGFR and EGFR, this pathway itself may provide multiple potential targets (1, 2). Among all the potential targets tested, the VEGFR pathway appears to be the most promising, followed by the EGFR and mTOR (mammalian target of rapamycin) pathways. Since multiple molecular pathways may be implicated in tumor cell growth, a combination of different agents may be able to target either multiple points within the same molecular pathway or certain points across multiple pathways. A combination of the anti-EGFR agent erlotinib (Tarceva®; Genentech, Roche, OSI Pharmaceuticals) and the anti-VEGF agent bevacizumab has been studied clinically, and an objective response rate of 21% was achieved (1, 2, 18). Further studies of combined therapy with the targeted agents and traditional immunotherapy are under way.

Conclusions

To determine whether the addition of other types of antitumor agents could improve the efficacy of traditional immunotherapy, especially IFN-α and IL-2, a number of studies have been carried out. Although the results of several clinical studies are sill pending, promising findings have been reported. Combination therapy with WX-G250 and low-dose IL-2 showed increased antitumor efficacy in the treatment of mRCC, with little toxicity. In a study in Denmark, combined therapy with IL-2 and HDC increased the survival rate in patients with mRCC, but further studies are needed to confirm these positive results. A clinical study performed in Japanese patients with advanced mRCC showed that combined immunotherapy with IFN-α and IL-2 resulted in a favorable response rate in the treatment of mRCC, with mild toxicity. Combined therapy with isotretinoin and IFN-α in the treatment of RCC also provided promising response rates, although this was associated with increased toxicity.

Recent advances in the understanding of the pathophysiological mechanisms of RCC have resulted in the identification of potential targets and to the rational design of corresponding targeted agents. Combination therapy with these targeted agents and traditional immunotherapy, *i.e*., bevacizumab, which targets VEGF, with IL-2, has shown very promising results. Further studies are under way.

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