NCCN Guidelines® Insights

Kidney Cancer, Version 2.2014

Featured Updates to the NCCN Guidelines

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Abstract

These NCCN Guidelines Insights highlight treatment recommendations and updates specific to the management of patients with advanced non–clear cell carcinoma included in the 2014 version of the NCCN Clinical Practice Guidelines in Oncology for Kidney Cancer. (*J Natl Compr Canc Netw* 2014;12:175–182)

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Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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The full and most current version of these NCCN Guidelines are available at NCCN.org.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Kidney Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Kidney Cancer

Disclosure of Relevant Financial Relationships

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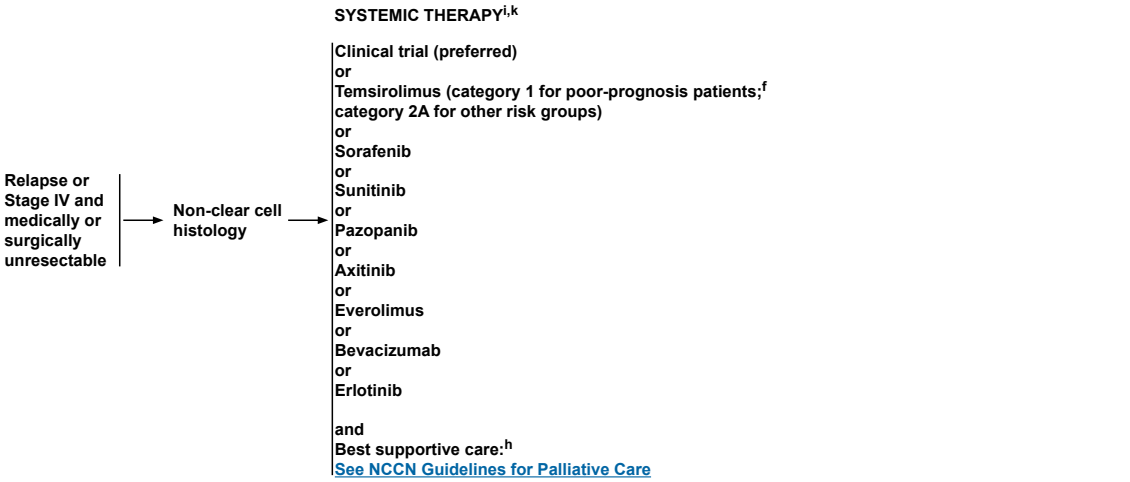

[f]Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-B).
[h]Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.
[i]Chemotherapy (category 3) in clear cell and non-clear cell RCC with predominant sarcomatoid features has shown modest response to gemcitabine + doxorubicin or gemcitabine + capecitabine.
[k]Partial responses have been observed to cytotoxic chemotherapy (carboplatin + gemcitabine or carboplatin + paclitaxel) with collecting duct or medullary subtypes.

KID-4

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

An estimated 63,920 Americans will be diagnosed with renal cancer and 13,860 will die of the disease in the United States in 2014.[1] Renal cell carcinoma (RCC) comprises approximately 3.9% of new cancers, with a median age at diagnosis of 64 years. The rate of RCC has increased by 1.7% per year for the past 10 years.[2] Approximately 90% of renal tumors are RCC, and 85% of these are clear cell tumors.[3] Other less common cell types include papillary, chromophobe, "translocation-type," and Bellini (collecting duct) tumors. Sarcomatoid features can occur in all histologic subtypes of RCC and do not present as a distinct entity. Medullary renal carcinoma is a variant of collecting duct renal carcinoma and was described initially as occurring in patients who are sickle cell trait–positive. Although there are distinct differences between the uncommon histological subtypes, they are usually grouped together as non–clear cell carcinomas in clinical studies.

Systemic Therapy for Patients With Non–Clear Cell Carcinomas

Clinical trials of targeted agents have predominantly focused on patients with clear cell versus non–clear cell histology because of the high prevalence of clear cell RCC. As detailed herein, some data indicate that targeted therapies approved for clear cell RCC may also have benefit for treating non–clear cell RCC. However, these benefits may be less than those for clear cell RCC.

mTOR Inhibitors

An established therapeutic target in RCC is mTOR, which is a central component of multiple converging cell signaling pathways regulating micronutrients, cell growth, apoptosis, and angiogenesis.[4–6] Two mTOR inhibitors, temsirolimus and everolimus, are FDA-approved for the treatment of patients with advanced RCC, although everolimus is approved in the United States for use after treatment failure with sorafenib or sunitinib. These 2 related drugs differ in route of administration and schedule. Temsirolimus is intravenously administered weekly, whereas everolimus is taken as a daily oral dose.

Temsirolimus

A retrospective subset analysis of the global Advanced Renal Cell Carcinoma (ARCC) trial found that temsirolimus showed a clinical benefit in patients (with poor prognostic features) with clear cell and non–clear cell histologies.[7,8] The median overall survival (OS) was 11.6 months with temsirolimus, compared with 4.3 months with interferon-α, in patients with non–clear cell RCC (predominantly papillary RCC).[8] This is the only reported phase III trial that included patients with RCC with non–clear cell histologies. Randomized clinical trials in rarer subgroups of patients are challenging.

Clinical trial data are lacking on temsirolimus in the treatment of patients with chromophobe RCC. A recent case report described a patient with metastatic chromophobe RCC refractory to sunitinib who experienced a response to temsirolimus for 20 months.[9]

Everolimus

The data on the benefit of everolimus in patients with non–clear cell RCC are limited. Data from subgroup analyses of an expanded-access trial and case reports support first-line use of everolimus in patients with non–clear cell RCC.[10–12]

The RAD-001 Expanded Access Clinical Trial in RCC (REACT) evaluated the efficacy and safety of everolimus in a subgroup of 75 patients with metastatic RCC of non–clear cell histology.[10] Note that median duration of treatment with everolimus was similar in the non–clear cell subgroup and in the overall REACT trial population (12 vs 14 weeks, respectively). Responses were rare (1.3% vs 1.7%) and rates of stable disease lasting at least weeks (49.3% vs 51.6%) were similar, suggesting similar cytostatic-type activity in clear and non–clear cell RCC.[10]

In a phase II study, 49 patients with non–clear cell RCC previously treated with sunitinib or sorafenib were given everolimus, 10 mg orally daily until disease progression or unacceptable toxicity.[12] The tumor histologies included papillary (n=29), chromophobe (n=8), collecting duct (n=2), sarcomatoid (n=4), and unclassified (n=6).[12] The median progression-free survival (PFS) was 5.2 months. The objective response rate was 10.2%, with all of the responses being partial. Twenty-five patients (51.0%) had stable disease; 16 patients (32.7%) experienced disease progression despite everolimus.[12] Interim results from an ongoing phase II trial (RAPTOR) suggest that everolimus (10 mg once daily) provides an antitumor effect in previously untreated patients with advanced papillary RCC. The median PFS as assessed by the investigators was 7.6 months (95% CI, 5.6–15.2). However, at the 2013 European Society for Medical Oncology (ESMO) annual meeting, central review showed a median PFS of only 3.7 months.[13]

Tyrosine Kinase Inhibitors

The tyrosine kinase inhibitors (TKIs) that bind to the tyrosine kinase domain of vascular epithelial growth factor (VEGF) receptors and also inhibit other tyrosine kinase–dependent receptors, including platelet-derived growth factor (PDGF) receptors, FMS-like tyrosine kinase 3 (FLT3), and stem cell growth factor (c-kit), inhibit the signaling associated with ligand binding of those receptors. Sunitinib,[14] sorafenib,[15] pazopanib,[16] and axitinib[17] of this family possess somewhat different kinase inhibition profiles and therapeutic indices in patients.

Sunitinib and Sorafenib

Data from expanded-access trials, phase II trials, and retrospective analyses support clinical activity of sunitinib[18–23] and sorafenib[24–26] in patients with non–

clear cell RCC, but with a rate lower than reported in clear cell RCC. Recent phase II trial data of 31 patients from Korea with non–clear cell RCC treated with sunitinib reported an overall response rate (ORR) of 36% (95% CI, 19%–52%) and median PFS of 6.4 months (95% CI, 4.2–8.6 months).[22] A second study of 57 patients with non–clear cell histology treated with sunitinib demonstrated a median PFS for 55 evaluable patients of only 2.7 months (95% CI, 1.4–5.4 months).[20]

Additional prospective studies are needed to further clarify the role of sunitinib and sorafenib in non–clear cell carcinoma. There are ongoing (ClinicalTrials.gov identifiers: NCT00465179 and NCT01108445) or recently completed (ClinicalTrials.gov identifier: NCT00979966) phase II studies investigating the role of sunitinib in non–clear cell carcinoma.

Pazopanib and Axitinib

The clinical benefit of pazopanib or axitinib has not yet been established in patients with non–clear cell carcinoma. There are ongoing clinical trials evaluating the efficacy of pazopanib and axitinib in patients with non–clear cell carcinoma in first-line and second-line settings (ClinicalTrials.gov identifiers: NCT01767636 and NCT01798446).

Erlotinib

The activity of erlotinib, an oral epidermal growth factor receptor TKI, was studied in patients with advanced papillary RCC.[27] Fifty-two patients were treated with oral erlotinib. The overall response rate was 11% (5 of 45 patients; 95% CI, 3%–24%), and the disease control rate (defined as stable disease for at least 6 weeks, or confirmed partial response or complete response using RECIST was 64%. The median OS was 27 months.[27]

Other Therapies for Patients With Non–Clear Cell Carcinomas

Bevacizumab is a humanized monoclonal antibody that binds and neutralizes all biologically active forms of VEGF-A. Bevacizumab inhibits angiogenesis in experimental models and growth of human tumor xenografts in vivo.[28,29] A small phase II trial studied bevacizumab monotherapy in patients with papillary RCC. The results in 5 accrued patients showed an encouraging activity in these patients. The PFS reported for each of these patients were 25, 15, 11, 10, and 6 months.[30] Further studies using bevacizumab is warranted in patients with papillary RCC.

Treatment of Specific Histologic Subgroups

Sarcomatoid RCC

Treatment of RCC with sarcomatoid features and non–clear cell histologies remains a challenge. Sarcomatoid variant is an aggressive form of RCC that can occur in any histology subtype but has mostly been reported as a high-grade component of clear cell RCC, and is associated with a poor prognosis and decreased responsiveness to the agents that benefit patients with clear cell RCC, including immunotherapies and the VEGFR and mTOR inhibitors.[31–35] Based on the activity of selected cytotoxic chemotherapies in soft tissue sarcomas, several small trials using chemotherapy regimens in patients with sarcomatoid RCC have been reported. Gemcitabine in combination with doxorubicin or capecitabine has been reported to show occasional responses, but better therapies need to be developed.[36–42]

Xp11 Translocation Carcinoma

Xp11 translocation carcinoma is a rare disease entity occurring almost exclusively in children and young adults, and may present with an aggressive clinical course in adults.[43] In a retrospective review, 15 adults with translocation carcinoma were identified, of whom 10, 3, and 2 received sunitinib, sorafenib, and monoclonal anti-VEGF antibodies, respectively. When treated with VEGF-targeted therapies, 3 patients experienced a partial response, 7 had stable disease, and 5 developed progressive disease. The median PFS and OS of the entire cohort were 7.1 months and 14.3 months, respectively.[44]

Medullary and Collecting Duct RCC

Among the non–clear cell histologies, renal medullary carcinoma is extremely rare, constituting approximately 2% of all primary renal tumors in young people, and is associated with sickle cell trait.[45,46] Metastatic disease is seen at presentation in 95% of the patients.[45,46] Chemotherapy, rather than targeted agents or immunotherapy, is generally offered to these patients, but the prognosis remains dismal because of poor response and multiple comorbidities.

Collecting duct carcinoma is also a rare type of non–clear cell RCC, often presenting at an advanced

stage of disease. Up to 40% of patients have metastatic spread at initial presentation, and most die within 1 to 3 years from the time of primary diagnosis.[47–50] Chemotherapy regimens used in the treatment of bladder cancer have been reported to achieve responses in collecting duct carcinoma. In a multicenter prospective study, 23 patients with no prior therapy were treated with a combination of gemcitabine and either cisplatin or carboplatin.[51] The results showed a response rate of 26% and an OS of 10.5 months.[51]

NCCN Recommendations for Patients With Non–Clear Cell Carcinomas

The NCCN Kidney Cancer Panel prefers enrolling patients with non–clear cell carcinoma in clinical trials when available (see KID-4, page 177). Data suggest that inhibition of the mTOR or VEGF pathway has shown clinical benefit in patients with non–clear cell carcinoma. Based on the significant improvement in OS seen in the subset analysis of the global ARCC trial involving mTOR inhibitors, the NCCN Kidney Cancer Panel has included temsirolimus as a treatment option for patients with non–clear cell carcinoma with poor prognosis features (category 1) and those with non–clear cell carcinoma in any other risk groups (category 2A). The panel also recently included everolimus as an option for patients with non–clear cell RCC (category 2A) based on data from subgroup analyses of an expanded access trial and case reports (see KID-4, page 177).

The TKIs sunitinib and sorafenib are also included as options for patients with non–clear cell carcinoma (category 2A), as are pazopanib (category 2A) and axitinib (category 2A) based on their similar mechanisms and therapeutic indices to sunitinib and sorafenib according to extrapolation of data from patients with clear cell histologies.

The panel recently included bevacizumab and erlotinib as single-agent options for patients with non–clear cell RCC (category 2A; see KID-4, page 177).

The panel notes that chemotherapy is a treatment option for clear cell and non–clear cell RCCs with predominant sarcomatoid features (category 3). The chemotherapy regimens that have shown some benefit for this patient population include gemcitabine in combination with doxorubicin or capecitabine. The panel also noted that partial responses to cytotoxic chemotherapy (gemcitabine in combination with carboplatin; paclitaxel in combination with carboplatin) have been observed in patients with other non–clear cell subtypes, such as collecting duct or medullary subtypes.

Conclusions

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) are in continuous evolution. They are updated annually, or sometimes more often if new high-level clinical data become available in the interim. The recommendations in the NCCN Guidelines, with few exceptions, are based on evidence from clinical trials. Expert medical clinical judgment is required to apply these guidelines in the context of an individual patient to provide optimal care. The physician and patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials.

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Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/40446;** and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet.

Posttest Questions

1. The less common cell types of RCC include
   a. Papillary
   b. Chromophobe
   c. Xp11 translocation
   d. Collecting duct
   e. All the above
   f. None of the above
2. The NCCN Kidney Cancer Panel has included temsirolimus as a treatment option for patients with non–clear cell carcinoma based on the significant improvement in the overall survival seen in the subset analysis of the
   a. Global ARCC trial
   b. The REACT trial
   c. Both the above
   d. None of the above
3. The NCCN Kidney Cancer Panel has included everolimus as an option for patients with non–clear cell RCC.
   a. True
   b. False