First-line Treatment of Metastatic Disease

Cisplatin-ineligible Patients

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KEYWORDS

• Urothelial carcinoma • Unfit for cisplatin • Prognostic factors • Carboplatin • Gemcitabine

KEY POINTS

- Patients not eligible for cisplatin are defined by one of the following: Eastern Cooperative Oncology Group performance status (PS) greater than or equal to 2, creatinine clearance (glomerular filtration rate [GFR]) less than 60 mL/min, hearing loss greater than or equal to grade 2, peripheral neuropathy greater than or equal to grade 2, heart failure greater than or equal to New York Heart Association class III.
- Patients unfit for cisplatin generally have a poor prognosis. Within this group PS 2, presence of visceral metastases, liver metastases, and low baseline hemoglobin are prognostic factors of poor outcome.
- Treatment decisions in patients who are unfit for cisplatin are mainly based on 2 factors: PS and renal function. In case of PS greater than or equal to 2 and GFR less than 60 mL/min, treatment consists of best supportive care or single-agent chemotherapy. In case of 0 or 1 risk factor, carboplatin-based combination chemotherapy is the preferred option with the highest level of evidence. Patient inclusion in clinical trials is highly recommended.

INTRODUCTION

Cisplatin-based combination chemotherapy is effective and can considerably improve outcomes in patients with advanced urothelial carcinoma (UC), with response rates of

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more than 50% and 5-year survival rates of 33% in patients with good performance status (PS; ie, Karnofsky score >80%) and no evidence of visceral metastases.[1,2] Patients fit for cisplatin, but with 1 or both of these poor prognostic factors, experience considerably worse outcomes.[1] Poor outcomes have also been shown when carboplatin is substituted for cisplatin. Although no adequately powered randomized trials have been completed comparing cisplatin-based with carboplatin-based chemotherapy combinations, a meta-analysis showed a significantly increased likelihood of achieving an objective response with cisplatin-based chemotherapy.[3] All practice guidelines therefore support the use of cisplatin-based regimens in advanced UC.[4,5] In clinical practice, greater than 50% of all patients with advanced UC have contraindications for treatment with cisplatin and alternative treatment options are necessary.[6] There is no consensus on the standard chemotherapy treatment of patients who are unfit for cisplatin.[4] This article reviews the definition of patients not eligible for cisplatin; clinical, pathologic, and molecular prognostic factors for this patient group; as well as different treatment options based on baseline patient characteristics.

DEFINING PATIENTS NOT ELIGIBLE FOR CISPLATIN

Although the human condition and the heterogeneity of disease necessitates a degree of vagueness and instinct in the practice of medicine, uniformly defining disease states, conditions, and end points is critical to drug development and integral to regulatory science. Several prior clinical trials, discussed in this article, have explored the development of therapeutic regimens in patients with metastatic UC who were considered ineligible for cisplatin.[7] However, these trials generally used variable eligibility criteria, complicating interpretation of the results. In 2011, an expert panel was convened to establish a uniform definition of cisplatin ineligibility to facilitate clinical trials in this patient population for the future.[8] Through consensus, this panel established the definition presented in **Box 1**. Although clinical judgment is essential when applying rigid guidelines such as these, to routine patient management, consistency in how patient populations are defined is critical for clinical trial purposes. The definition shown in **Box 1** has been adopted in the design of several ongoing clinical trials.

PROGNOSTIC FACTORS IN PATIENTS NOT ELIGIBLE FOR CISPLATIN

Similar to cisplatin-eligible patients with metastatic UC, cisplatin-ineligible patients also represent a heterogeneous group with variable outcomes to treatment. Several

Box 1
Consensus definition of cisplatin ineligibility for clinical trial design

At least 1 of the following:

- ECOG PS of 2 (KPS of 60%–70%)
- Creatinine clearance less than 60 mL/min
- CTCAE v4 grade greater than or equal to 2 audiometric hearing loss
- CTCAE v4 grade greater than or equal to 2 peripheral neuropathy
- NYHA class III heart failure

Abbreviations: CTCAE v4, common terminology criteria for adverse events, version 4; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; NYHA, New York Heart Association.