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Use of Chemotherapy in Advanced Unresectable or Metastatic Transitional Cell Carcinoma of the Bladder or Urothelium Practice Guideline Report #3-12

Members of the Genitourinary Disease Site Group

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SUMMARY

Guideline Question

What is the optimal chemotherapeutic regimen for patients with advanced unresectable or metastatic cancer of the bladder or urothelium? Overall and progression-free survival, toxicity, quality of life, and clinical improvement are the outcomes of interest.

Target Population

These recommendations apply to adult patients with advanced unresectable or metastatic transitional cell carcinoma of the bladder or urothelium.

Recommendations*

- Chemotherapy with gemcitabine-cisplatin (GC) or dose-intense methotrexate, vinblastine, doxorubicin, and cisplatin given with granulocyte-colony stimulating factor (DI-MVAC + G-CSF) should be offered to patients with advanced unresectable or metastatic cancer of the bladder or urothelium for the purpose of improving survival.
- Standard MVAC without G-CSF (S-MVAC) remains a chemotherapeutic option and provides similar survival benefits to GC or DI-MVAC + G-CSF but with higher risks of toxicity, including toxic death. In a recent large randomized trial comparing GC with S-MVAC, statistically and clinically significant differences in toxicity favouring GC over S-MVAC were seen; rates of neutropenic sepsis, mucositis, and unfavourable effects on weight were significantly less with GC. Similar significant differences in toxicity were observed in another large randomized trial that compared DI-MVAC + G-CSF with S-MVAC; in this trial, rates of severe leukopenia, neutropenic fever, and mucositis were significantly less with DI-MVAC + G-CSF compared with S-MVAC.
- Chemotherapy with cisplatin-methotrexate-vinblastine (CMV) is a reasonable alternative for patients who cannot receive doxorubicin or gemcitabine therapy, but has toxicities similar to those of S-MVAC.

* Details of dose and schedules for recommended treatment regimens are provided in Appendix 1 of the full Practice Guideline Report.

Qualifying Statements

- This guideline does not apply to patients with superficial or locally advanced transitional cell carcinoma of the bladder or bladder cancer of non-transitional histology.

Methods

Entries to MEDLINE (1996 through November 2000), CANCERLIT (1983 through October 2000), and Cochrane Library (2000, Issue 4) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997-2000) were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected by one member and reviewed by three members of the Practice Guidelines Initiative's Genitourinary Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Genitourinary Cancer Disease Site Group, which comprises medical and radiation oncologists, urologists, and two patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- S-MVAC and CMV have demonstrated improved response, progression-free survival, and overall survival rates when compared with control chemotherapy regimens in randomized trials. Toxicity associated with S-MVAC and CMV is not inconsequential and toxic death rates up to five percent have been reported.
- Combination chemotherapy with S-MVAC, GC, and DI-MVAC + G-CSF provides similar overall and progression-free survival outcomes. One large trial comparing GC with S-MVAC detected an equivalent response rate and no statistically significant difference in overall survival (median survival, 13.8 months versus 14.8 respectively; hazard ratio [HR], 1.04; 95% CI, 0.82-1.32; $p=0.75$). Another trial, published in abstract form, detected a superior response rate and no statistically significant difference in two-year survival with DI-MVAC + G-CSF when compared with S-MVAC (35% versus 25%, respectively; HR, 0.80; 95% CI, 0.60-1.06; logrank $p=0.1218$)
 - Toxicity risks differ among chemotherapy regimens with reported toxic death rates of up to five percent with S-MVAC, one percent with GC, and three percent with DI-MVAC + G-CSF.
 - GC was associated with significantly less neutropenic sepsis (1% versus 12%, $p<0.001$), grade 3 or 4 mucositis (1% versus 22%, $p=0.001$), and unfavourable effects on weight (weight gain $\geq 5\%$ from baseline, 12% versus 3%; $p=0.002$ and weight loss $\geq 5\%$ from baseline, 8% versus 16%; $p=0.02$) compared to S-MVAC. Clinically important differences favouring GC were observed in rates of grade 4 neutropenia (30% versus 65%), neutropenic fever (2% versus 14%), and grade 3 or 4 alopecia (11% versus 55%). GC was associated with more grade 3 or 4 anemia (27% versus 18%) and asymptomatic thrombocytopenia (57% versus 21%) than S-MVAC.
 - DI-MVAC + G-CSF was associated with significantly less grade 2 to 4 leukopenia (41% versus 84%, $p<0.001$), neutropenic fever (10% versus 26%, $p<0.001$), and grade 3 or 4 mucositis (10% versus 17%, $p=0.034$), but more asymptomatic grade 2 to 4 thrombocytopenia (38% versus 29%, $p<0.033$) compared to S-MVAC.

Future Research

As most patients with advanced unresectable or metastatic cancer of the bladder or urothelium die of the disease within two years of diagnosis despite the use of cisplatin-based combination chemotherapy, these patients should continue to be encouraged to participate in controlled clinical trials studying novel agents and drug combinations.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Report #3-2-1: *Use of Adjuvant Chemotherapy Following Cystectomy in Patients with Deep Muscle-Invasive Transitional Cell Carcinoma of the Bladder.*

For further information about this practice guideline report, please contact Dr. Himu Lukka, Chair, Genitourinary Cancer Disease Site Group, Hamilton Regional Cancer Centre, 699 Concession Street, Hamilton ON, L8V 5C2; TEL (905) 387-9711 ext. 54703; FAX (905) 575-6326.

*The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.*

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to enable evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, community representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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