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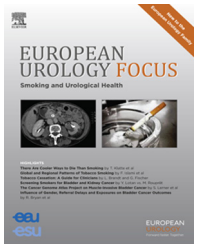

Testis Cancer

Consensus Recommendations from the Spanish Germ Cell Cancer Group on the Use of High-dose Chemotherapy in Germ Cell Cancer

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Abstract

Background: High-dose chemotherapy (HDCT) has been studied in several clinical scenarios in advanced germ cell cancer (GCC).
Objective: To establish a clinical practice guideline for HDCT use in the treatment of GCC patients.
Design, setting, and participants: An expert panel reviewed information available from the literature. The panel addressed relevant issues concerning and related to HDCT. The guideline was externally reviewed by two international experts.
Results and limitations: The efficacy of HDCT has been demonstrated in selected GCC patients. The most conclusive evidence comes from retrospective analyses that need to be interpreted with caution. HDCT can cure a significant proportion of heavily treated GCC patients. When indicated, sequential HDCT with regimens containing carboplatin and etoposide, as well as peripheral stem-cell support, is recommended. There is no conclusive evidence to recommend HDCT as first-line therapy. According to a multinational retrospective pooled analysis, HDCT might be superior to conventional CT as first salvage treatment in selected patients. There is an urgent need for prospective clinical trials addressing the value of HDCT in GCC patients who experience failure on first-line cisplatin-based CT. In patients who progress on conventional-dose salvage CT, HDCT should be considered. Treatment of these patients at experienced centers is strongly recommended.
Conclusions: It has been demonstrated that HDCT cures selected GCC patients who experience disease progression on conventional rescue regimens. The panel recommends the inclusion of GCC patients in randomized clinical trials including HDCT.
Patient summary: This consensus establishes clinical practice guidelines for the use and study of high-dose chemotherapy in patients with germ cell cancer.

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1. Introduction

Almost 30–40% of patients with advanced germ cell cancer (GCC) with poor prognosis according to the International Germ Cell Consensus Classification and treated with cisplatin-based chemotherapy experience failure of initial cisplatin-based chemotherapy [1]. Conventional-dose chemotherapy (CDCT) given as salvage treatment includes regimens that contain cisplatin and ifosfamide plus etoposide, vinblastine, or paclitaxel, and is effective in patients with favorable risk features such as primary gonadal tumors and good response to previous first-line chemotherapy (Supplementary Tables 1 and 2) [2–6,46–48]. However, most GCC patients treated with CDCT will succumb to the disease; the 5-yr overall survival (OS) is 40.8%, and ranges from 64.5% to 3.5% according to risk group [7]. It should also be noted out that almost two-thirds of patients have intermediate-risk or high-risk disease [8].

HDCT use can be summarized in three categories: first-line up-front therapy in patients with poor prognosis; first salvage therapy; and second or subsequent salvage therapies. Since the introduction of HDCT as an effective salvage therapy in heavily pretreated GCC patients [9], several retrospective studies have demonstrated cure in more than 30% of patients, even in the presence of very adverse prognostic features [6,10–12]. However, prospective randomized clinical trials in earlier disease have failed to demonstrate a consistent improvement in survival for HDCT [13–15]. Several differences in patient selection and treatment characteristics, including chemotherapy agents and the number of HDCT cycles administered, make it difficult to interpret the results and guide clinical decisions.

A large international retrospective pooled-data analysis [7] suggested a benefit for HDCT over CDCT as first-line salvage therapy, with a 35% reduction in the risk of death. This encouraging study prompted the development of an intergroup prospective randomized trial comparing HDCT to CDCT for first salvage treatment.

This consensus came into being as a response to uncertainty in the field of salvage therapy perceived by members of the Spanish Germ Cell Cancer Group (SGCCG). In addition, the initiative is in line with a proposal by Spanish health care authorities on defining referral centers for the treatment of relapsed GCC.

Here we suggest a clinical guideline for treatment of GCC patients with HDCT. To focus on the most relevant topics, an expert panel was convened and asked to review current evidence based on previously selected questions.

1.1. Guideline questions

Q1: Is there a benefit for the use of HDCT with stem-cell support in GCC patients?
Q1A: HDCT in first-line up-front regimens.
Q1B: HDCT as first-salvage treatment.
Q1C: HDCT as second or subsequent salvage therapy after progression on CDCT.
Q2: What tools are available to predict tumor evolution in patients with GCC relapse?
Q3: What is the preferred therapy for GCC patients who fail on first-line cisplatin-based chemotherapy?
Q4: Regarding access to salvage therapy among GCC patients:
Q4A: Should salvage treatment be delivered at highly experienced centers?
Q4B: Is HDCT accessible to all centers treating GCC?
Q5: What is the preferred HDCT regimen for treatment of GCC patients with relapse?
Q6: Is there a role for salvage surgery after HDCT?

2. Materials and methods

2.1. Panel composition and external experts

The SGCCG steering committee convened an expert panel consisting of clinical oncologists with experience in the treatment of patients who experience failure of first-line cisplatin-containing chemotherapy. The steering committee selected panel members from the SGCCG member directory on the basis of contributions to current and previous GCC studies.

The steering committee asked two external experts to review and provide comments on the consensus document. External experts working in a health care system similar to the Spanish system and with relevant contributions in the field were selected. The experts' comments were reviewed and accepted by all panel members.

2.2. Literature review and analysis

2.2.1. Literature review

The MEDLINE and EMBASE databases were searched for evidence published from 1990 to September 2015. Articles were selected for inclusion in the review if they were fully published in the English language and reported evidence in GCC patients with failure on cisplatin-based chemotherapy or included treatment with HDCT in GCC. One reviewer selected the most relevant evidence for the expert panel. Panel members provided additional evidence when needed (Supplementary Fig. 1).

2.2.2. Data analysis

Primary outcome measures included OS, disease-free survival (DFS), and treatment-related toxicities. Data were extracted into evidence tables (Supplementary Tables 1–7) by one reviewer and checked for accuracy by a second reviewer. Disagreements were resolved by discussion and by consultation with the expert panel co-chairs if necessary.

2.3. Consensus development based on evidence

The expert panel met to review the evidence and formulate guideline recommendations. Three members participated in the preparation of the draft guideline and all members reviewed the guideline document. Two international experts were invited to review the guideline document.

2.4. Guideline and conflicts of interest

Members of the panel completed a disclosure form, including any financial or other relevant relationship relevant to the guideline.

2.5. Revision dates

If necessary, the panel plans to reconvene to discuss potential changes. When appropriate, the panel will recommend revised guidelines to the SGCCG.

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