SUN 430

Expert Panel Recommendations for the Management of Patients with Persistent and Recurrent Cushing's Disease

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* Potential conflict of interest may exist. Please refer to the Meeting App.

BACKGROUND

- Consensus guidelines are limited for management of persistent or recurrent Cushing's disease (CD).
- The RAND/UCLA modified Delphi process is a group decision-making method that systematically establishes the appropriateness of a wide variety of medical approaches.

OBJECTIVE

- To develop consensus statements on the management of persistent or recurrent CD patients.

METHODS

- Modified RAND/UCLA Delphi process was used to elicit expert consensus, which involved rating of clinical patient scenarios by experts, quantitative summary of panel agreement, and development of consensus statements.

Panelists

- 11 endocrinologists, experts in management of CD, from diverse locations in the US and several practice types.

Development of Clinical Patient Scenarios in CD

- 708 clinical treatment scenarios were constructed based on key variables selected by the experts, which included hypercortisolism, size of pituitary adenoma, hypopituitarism, desire for fertility, diabetes, liver function status, and overall CD health status.
- All described patients were assumed to have access to appropriate care, to have undergone initial pituitary surgery, and not to have pituitary tumors abutting the optic chiasm.
  - Clinical descriptions of patients were assumed to be defined according to the treating clinician's judgment and his/her institutional or laboratory standards.

Rating of Clinical Patient Scenarios

- Experts rated the appropriateness for different treatments on a 1-9 scale as the **initial treatment** in patients with residual/recurrent CD.
- Experts submitted ratings before and after an in-person panel discussion to clarify definitions.
- Treatment was defined as appropriate (median rating: 7-9), least desirable (median rating: 1-3), or uncertain (median rating: 4-6), with no disagreement.
  - Disagreement was defined as >2 ratings from 1-3 and >2 from 7-9.
- Consensus statements were developed based on final ratings.

RESULTS

- 11 panelists had practiced medicine a median of 29 years, spent about 50% of their time in clinical care, and about 25% conducting research.
- Agreement increased from 82.1% (581 scenarios) pre- to 97.5% (690) post-meeting, with 43.4% of treatment scenarios rated appropriate, 21.6% rated uncertain, and 32.5% rated least desirable.

CONSENSUS STATEMENTS

Medical Therapy

Medical therapy is nearly always useful to consider as one possible initial treatment of persistent or recurrent CD.

- Ketoconazole can be used in patients with any degree of cortisol excess or size of tumor. It should be avoided in patients with transaminase levels at or above three times the upper limit of normal.
- Cabergoline and metyrapone are useful in patients with mild or moderate hypercortisolism without fulminant disease and may be used in patients with severe hypercortisolism. Mifepristone may also be an option in these settings.
- Pasireotide can be used in patients with invasive or aggressive macroadenomas and mild/moderate hypercortisolemia or severe hypercortisolemia without fulminant disease.[1]
- Etomidate, mitotane, and temozolomide are not typically used as initial treatment of persistent or recurrent CD.
- In the life-threatening circumstance of severe hypercortisolism with fulminant disease, all medications providing a good chance of prompt biochemical control should be considered, including the use of multiple medications in combination (such as ketoconazole plus metyrapone) or an etomidate infusion in the inpatient setting.[2]

[1] Panelists disagreed about the use of pasireotide with mild/moderate without fulminant disease as a first medication, but agreed that it is likely to be effective with milder biochemical abnormalities.

[2] Some medications are much more appropriate (e.g., etomidate, ketoconazole, metyrapone) and others less appropriate (e.g., cabergoline, pasireotide) for severe hypercortisolism with fulminant disease, and up to 4 medications may be needed.

Radiotherapy and Surgery

Radiation therapy, repeat pituitary surgery, or bilateral adrenalectomy may be useful to consider as initial treatment of persistent or recurrent CD.[1]

- Radiation therapy, when given with medical therapy, is nearly always useful to consider as initial treatment of persistent or recurrent CD.[1]
- If residual tumor is identified, and an expert pituitary surgeon believes it may be excised, repeat pituitary surgery is nearly always useful to consider as initial treatment of persistent or recurrent CD.
- Bilateral adrenalectomy can be used as treatment of persistent or recurrent CD in patients with severe hypercortisolism with fulminant disease.

[1] Because of the delayed effect of radiation, biochemical control with medical therapy is needed in the interim.

RESULTS (CONT.)

Pregnant Patients

In pregnant patients with persistent or recurrent CD, joint management with a maternal-fetal medicine specialist (perinatologist or high-risk obstetrician) is recommended.

- Observation without treatment may be appropriate in pregnant patients who have mild hypercortisolism and a microadenoma.
- Repeat pituitary surgery may be used for pregnant patients with persistent or recurrent CD regardless of disease severity. Decisions around timing of surgery should be made in conjunction with a high-risk obstetrician.
- Medical treatment may be used in pregnant patients who have moderate or severe hypercortisolism.
- Though there are no medical therapies approved for initial treatment of persistent or recurrent CD in patients who are pregnant, metyrapone is commonly used.
- Mitotane and mifepristone are contraindicated in pregnancy.

- Treatments not mentioned may be used if initial treatment has been tried and failed.

LIMITATIONS

- Although the Delphi panel method has been shown to be reproducible, a different panel composition may have developed different statements.
- The Delphi panel process does not develop new information.

CONCLUSIONS

- **The best approach in a given patient will vary depending on the exact circumstances.**
- **Panelists emphasize that the optimal treatment approach involves shared decision-making with the patient, endocrinologist, and neurosurgeon, and requires weighing multiple factors, including patient preferences; size, location and characteristics of residual tumor; concurrent medication use; drug interactions; cost; and the availability of expert care.**

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