

Hormonal Therapy in Palliative Setting

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Hormones are commonly used in palliative care. The two major indications are: (1) sensitive tumours such as breast cancer or prostate cancer and (2) symptoms that are thought to be responsive to hormones. Corticosteroid is commonly used for the latter purpose.

Corticosteroids have been used in a variety of situations (table 1) but few randomized studies have been performed because of difficulty in accrual of patients and compliance with study protocols. The randomized study by Hardy ² failed to show an advantage of corticosteroid over placebo for patients with intestinal obstruction. One of the explanations for the negative result was a small sample size.

Table 1: Situations where corticosteroids have been used

Anorexia
Asthenia
Brain tumours
Cachexia
Dermatomyositis
Dysphagia
Dyspnoea
Hypercalcaemia
Intestinal obstruction
Liver tumour
Nausea and vomiting
Neuropathic pain
Pruritus
Spinal cord compression
Stridor
Superior vena cava obstruction

Although corticosteroids are frequently used, side effects are common. These include neuropsychological disturbance, hyperglycemia, fluid retention and gastrointestinal disturbance, Cushing's syndrome, weight gain, hypertension, peptic ulcer, osteoporosis, myopathy and infections. To use corticosteroids effectively, there should be an accurate diagnosis, a clear treatment goal and frequent monitoring of response and side effects. Corticosteroids should be stopped if the intended goal is not achieved.

Breast cancer responds to chemotherapy and hormones. The choice depends on stage, histology and receptor status of the tumour; speed of disease progression; response to

previous therapy; type, and severity of symptoms; general condition of the patient and menopausal status. Tamoxifen, an anti-oestrogen with partial agonist effect, is commonly used as first line hormonal therapy. It acts by competing with oestradiol for oestrogen receptors. The usual dose is 20mg once a day orally. Present evidence indicates that a higher dose is not more effective. Common side effects include hot flush, vaginal dryness or discharge. Symptoms may exacerbate when tamoxifen is started. This is attributed to the partial agonist action of the drug and known as ‘tumour flare’. Tamoxifen may cause menstrual disturbance in premenopausal women. It is also associated with an increased risk of endometrial cancer. This may have less relevance in palliative care where patient’s life expectancy is limited.

Megesterol acetate has been used as second line hormonal agent. It acts on progesterone receptors and indirectly on pituitary/adrenal and pituitary/ovarian axes. The usual dose is 160mg once a day orally. Non-randomized trials suggest a dose response relationship but this has not been confirmed by randomized trials. Side effects include nausea, fluid retention, weight gain and vaginal bleeding. Thromboembolism is rare. It has also been used for patients with anorexia and cachexia.

Aromatase inhibitors (table 2) act on the enzyme aromatase, which is responsible for the final step of estrogen synthesis: the conversion of androstenedione and testosterone to estrone and estradiol. Their use has been limited by their side effects. The classical agent aminoglutethimide causes lethargy, orthostatic hypotension, nausea, vomiting, hypothyroidism, reversible agranulocytosis, and skin rash. Newer agents have fewer side effects and they have established a role as second line hormonal treatment for postmenopausal women with metastatic breast cancer.

Table 2: Classification of aromatase inhibitors

Generation	Non-steroidal (type 1)	Steroidal (type 2)
1 st	Aminoglutethimide	
2 nd	Rogletimide Fadrozole	Formestane
3 rd	Anastrozole Letrozole Vorzole	Exemestane

Though hormones are commonly used, some issues remain unclear. First, opinion varies on the optimal first line hormonal treatment for premenopausal women with advanced or metastatic breast cancer. Choices include tamoxifen, LHRH analogue, ovarian irradiation or oophorectomy. Second, it is not yet known whether combined hormonal treatment is superior to monotherapy. A recent meta-analysis by the EORTC (3) showed that the combination of LHRH analogue with tamoxifen was superior to LHRH analogue alone in terms of response rate, progression free survival and overall survival. The author has named such approach as ‘maximal oestrogen blockade’ but this approach is not yet widely accepted.

For patients with advanced prostate cancer, orchidectomy remains the gold standard. A 90% reduction in serum testosterone level has been observed within 12 hours of orchidectomy. Side effects include surgical complications, hot flushes, impotence, osteoporosis and psychological disturbance.

Oestrogen is another option. It acts on pituitary to suppress secretion of LH and acts

directly on prostate and testes. Side effects include thromboembolism, impotence, loss of libido, gastrointestinal disturbance and gynaecomastia. A common regimen is fofestrol 120mg twice a day orally.

LHRH analogue acts by stimulating pituitary secretion of LH followed by desensitization. Its effectiveness has earned its name of 'medical castration'. However, its initial stimulatory action may trigger 'tumour flare', which refers to a transient exacerbation of symptoms. Other side effects include hot flushes, loss of libido and impotence. LHRH analogue has been criticized for its high cost.

Anti-androgens are classified into steroidal and non-steroidal types. Cyproterone acetate is a steroidal anti-androgen with progestational activity. Its side effects include thromboembolism and significant loss of libido. Flutamide is a non-steroidal anti-androgen, sometimes referred as 'pure anti-androgen'. It has fewer side effects and it is usually used for patients who have been treated previously by orchidectomy.

Combined androgen blockade, also known as maximum or total androgen blockade, aims at improving treatment results by combinations such as flutamide with orchidectomy or LHRH analogue. The meta-analysis by the Prostate Cancer Trialists' Collaborative Group, however, failed to show advantage for this approach over monotherapy (4). Opinion is also divided on whether to start hormone immediately or defer it until symptom progresses. The role of flutamide as a second line agent has recently been challenged by the EORTC trial (1) which showed a superiority of prednisolone 5mg qid over flutamide 250mg tid in terms of quality of life parameters while time to progression, overall survival, PSA and subjective response rates were comparable.

Besides breast and prostate cancers, hormonal treatments have also been used for endometrial cancer, primary liver cancer, ovarian cancer, pancreatic carcinoma, renal cell carcinoma, melanoma and glioma. However, the role in these situations is not well defined.

In summary, though hormonal treatments are commonly used in palliative care, some areas, such as their effectiveness on specific symptoms, need further investigation. Like other areas of palliative care, researches are limited by the lack of effective methodology. Development of new approaches would be necessary.

References:

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