Journal Watch

A Pilot Study Evaluating the Safety and Efficay of Modafinil for Cancer-Related Fatigue

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Reference: Blackhall L *et a*l
Journal of Palliative Medicine Vol 12, No. 5, May 2009

Purpose: Cancer-related fatigue (CRF) is a common symptom, which can significantly lower the QOL in palliative patients with cancer. The persistent tiredness can manifest itself physically and or mentally and is often associated with depression and reduced functional status. Psychostimulants are used to treat CRF with methylphenidate being the most studied, but there are significant side effects associated with its use. Modafenil is FDA approved for the treatment of narcolepsy and has been used in MS related fatigue. Its MOA is not known, but appears to be more selective to the sleep-wake centers of the brain.
The purpose of the study was to evaluate to tolerability and efficacy of modafenil.

Method: Eligible patients had to have a cancer diagnosis and ECOG functional status of 1-3. Brief Fatigue Inventory (BFI) of at least 4. TSH levels WNL and able to provide consent had to be non-pregnant and over 18. Patients were excluded if fatigue was due to reversible causes such as hypothyroidism, anemia or hypercalcemia.Eligible patients were assessed for fatigue with BFI, depression with HADS, QOL with FACT-BR. Functional status was measured with ECOG and Barthel Index and neurocognitive with HVLT, Grooved Pegboard Test, COWAT, Trail A & B. NCI Common Toxicity criteria was used to evaluate severity of side effects.26 patients were required to adequately power the study.

Results: 27 patients registered (1 died prior to initiation) ECOG scores 1 (37%), 2 (44%)& 3 (19%).Grade 2 toxicities: auditory, sinus tachycardia, fatigue, nausea, dizziness (3) insomnia, blurry vision, abdominal pain, headache (3)
Grade 3: dyspnea.Change in BFI was primary outcome. 46% had improvement at week 2 and 75% at week 4. (p= 0.025). QOL improved as did depression. Neurocognitive function was not significantly changed.Functional status using Barthel's Index did not improve significantly (the scores were high at baseline) but there was improvement in ECOG and no deterioration was seen.

Discussion: CRF is multifactorial and not completely understood. Some causes such as hypercalcemia can be treated whereas others (effects from chemo, RT & necessary meds) cannot.This study showed modafenil is well tolerated and side effects mild. 75% reported improvement in primary outcome in 4 weeks. Depression, QOL and functional status scores improved but the neurocognitive scores did not, which surprised the authors who feel this may be due to Type I error.

Strengths of Study:
Prospective trial measuring numerous outcomes using validated tools.
Statistically significant data suggests a treatment safety and efficacy, which should be confirmed in larger more robust trials.

Limitations of Study:
Sample size and open-label one-arm design, with multiple opportunities for biases.
The trial was powered sufficiently to show a 30% decrease in BFI but not necessarily the neurocognitive changes.
The authors did not specifically detail patient characteristics, therefore it is difficult to determine whether the study applies to out patient population.

Relevance to Palliative Care:
CRF is a common symptom in cancer patients including the palliative population. Currently, treatment is limited to methylphenidate, the least toxic of the psychostimulants. Modafenil promises to be a safer and efficacious alternative. Although we will have to await the results of larger trials, modafenil may be considered when methylphenidate is not an option due to toxicities.