FATIGUE: PHARMACOLOGICAL AND NON-PHARMACOLOGICAL TREATMENT

Fausto Roila
Medical Oncology Division, Terni, Italy
CONFLICT OF INTERESTS

NO CONFLICT
FATIGUE: DEFINITION (ASCO, NCCN)

Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning.

In comparison to the fatigue experienced by healthy individuals, cancer-related fatigue is often not alleviated by rest or sleep.
FATIGUE: INCIDENCE

Cancer-related fatigue can occur before, during and even long after anti-cancer treatment has been completed

- up to 40% of pts report fatigue at diagnosis
- 80% and 90% of pts during chemotherapy and radiotherapy, respectively
- 17%-53% of pts in the post-treatment phase
FATIGUE: ETIOLOGY

- The underlying mechanisms for CRF has not been fully elucidated

- **Current hypotheses:** fatigue is correlated to elevations in levels of proinflammatory cytokines, 5-hydroxytryptophan dysregulation, hypothalamic-pituitary-adrenal axis dysfunction, circadian rhythm disturbances, and increased vagal tone
FATIGUE: DETERMINANTS

TUMOUR-RELATED FACTORS AND COMPLICATIONS Anemia, electrolyte abnormalities, dehydration, renal, liver or hearth failure, anorexia/cachexia, adrenal insufficiencies, fever.

PHYSICAL SYMPTOMS ASSOCIATED TO TUMOUR OR ITS TREATMENT Pain, dyspnea, difficulty swallowing, appetite loss

COMORBID CONDITIONS Hypothyroidism, diabetes mellitus, COPD, cardiovascular disease, infections
FATIGUE: DETERMINANTS

PSYCHOLOGICAL/BEHAVIOURAL FACTORS
Anxiety, depression, sleep disorders, decreased physical activity

SIDE EFFECTS OF OTHER MEDICATIONS
Opioids, psychiatric drugs, antihistamines, beta blockers, corticosteroids

IATROGENIC FACTORS
Chemotherapy, radiotherapy, surgery, immunotherapy, hormonal therapies, small-molecule targeted therapies
TREATMENT-ASSOCIATED FATIGUE IN CANCER PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS: A SYSTEMATIC REVIEW AND META-ANALYSIS

RESULTS

- 17 randomised phase II and III trials in cancer pts treated with ipilimumab, nivolumab, pembrolizumab and tremelimumab were considered eligible

- Compared with control regimens the odds ratio for all-grade fatigue for CTLA-4 inhibitors was 1.23 and for high-grade fatigue was 1.72.

- On the other hand, the odds ratio for all-grade fatigue for PD-1 inhibitors was 0.72 and for high-grade fatigue was 0.36
FATIGUE: SCREENING AND DIAGNOSIS

- All cancer pts should be screened for fatigue at their initial clinical visit, and then regularly during and after their anti-cancer treatment has ceased.

- If on initial screening a pt refers fatigue an assessment of its intensity using either a uni-dimensional (e.g., the Visual Analogue Fatigue Scale or the Brief Fatigue Inventory) or a multi-dimensional tool (e.g., the Multidimensional Fatigue Inventory or the Functional Assessment of Cancer Therapy-Fatigue scale [FACT-F]) should be performed.
FATIGUE: TREATMENT

- Identify and, possibly correct, contributing factors impacting on fatigue (i.e., adjusting the anticancer treatment or dose, correcting anemia, hypercalcemia and other metabolic abnormalities, treating anorexia-cachexia, anxiety, depression, pain, dyspnea, etc.)
FATIGUE: PHARMACOLOGICAL INTERVENTIONS

- PSYCHOSTIMULANTS (methylphenidate, dexamethyphenidate, dexamphetamine, modafinil, armodafinil)
- ANTIDEPRESSANTS
- ACETYLCOLINE INHIBITORS
- CORTICOSTEROIDS
- L-CARNITINE
- COENZIME Q₁₀
PSYCHOSTIMULANTS

- 19 RCT with fatigue as primary endpoint (11 with methylphenidate, 4 with modafinil, 3 with armodafinil and 1 with dexamphetamine) have been published.

- 15 trials showed no superiority of psychostimulants with respect to placebo, while 4 studies showed less fatigue with methylphenidate with respect to placebo.
PSYCHOSTIMULANTS

- A subgroup analysis suggested some benefit in the control of severe fatigue in 2 trials (1 with methylphenidate and 1 with modafinil).

- Therefore the efficacy of psychostimulants in the control of cancer-related fatigue is not clearly demonstrated.
PSYCHOSTIMULANTS

- In several trials the study was interrupted before reaching the determined sample size (10 of the 19 studies) often for refusal of pts to participate in the study.

- A loss of enrolled pts after randomization of more than 15% was shown in 12 of the 19 studies.
PSYCHOSTIMULANTS

- Therefore, more well planned studies with a larger number of pts are necessary to define the role of psychostimulants in cancer-related fatigue

- These studies should always be placebo-controlled studies; in fatigue control, the placebo has an important role
PSYCHOSTIMULANTS

- It is necessary to study a more selected pt population (e.g., pts with moderate-severe or with only severe fatigue, the impact in this subgroup of psychostimulants remains to be defined; pts submitted to CT, or to RT, or terminal cancer pts)
TREATMENT: ANTIDEPRESSANTS

- Two double-blind controlled studies evaluating paroxetine 20 mg/day vs placebo in pts submitted to chemotherapy reporting fatigue have been published

- Both studies did not show a reduction of fatigue with antidepressant with respect to placebo. On the other hand, depression ameliorated with paroxetine
TREATMENT: ACETYLCHOLINESTERASE INHIBITORS

- Donepezil 5 mg at day for 7 days, has been evaluated in a double-blind study with respect to placebo in 103 metastatic cancer pts reporting fatigue ≥ 4.

- This study did not show differences in efficacy and tolerability between the two arms
TREATMENT: CORTICOSTEROIDS
(Yennurajalingam S, J Clin Oncol 2013; 31: 3076-82)

- This is a double-blind randomized study comparing dexamethasone (4 mg bid for 14 days) versus placebo in 84 terminal cancer pts with fatigue ≥ 4

- Dexamethasone reduced significantly fatigue and ameliorated quality of life (physical symptoms)

- Adverse events were not significantly different
TREATMENT: L-CARNITINE

- A double-blind study comparing L-carnitine versus placebo in 376 pts submitted to radiotherapy or chemotherapy for metastatic cancer reporting fatigue has been published.

- L-carnitine 2 g/day for 4 weeks did not improve fatigue with respect to placebo (result similar were observed in 33% of pts presenting carnitine deficit).

- Even pain and depression were not influenced by L-carnitine.
TREATMENT: COENZYME Q\textsubscript{10}

- A double-blind study comparing coenzyme Q10 versus placebo in 236 pts with breast cancer submitted to chemotherapy has been reported

- Coenzyme Q\textsubscript{10} 100 mg tid, associated to vitamin E 100 mg tid, did not show a reduction of fatigue or a better quality of life
PHARMACOLOGIC TREATMENT: CONCLUSIONS

- All studied drug for cancer-related fatigue, with the exception of dexamethasone in terminal cancer pts, obtained negative results.

- It is necessary to better identify neuroreceptors involved in the fatigue (to personalize therapy)

- It is necessary to study more selected pt population (e.g., pts with moderate-severe or only severe fatigue; pts submitted to CT, or to RT, or terminal cancer pts)
PHARMACOLOGICAL TREATMENT: CONCLUSIONS

- Combinations of pharmacologic and non pharmacologic interventions (mind-body interventions such as agopuncture, yoga, ginseng; physical activity and psychological interventions such as cognitive behavioral therapy) should be evaluated.
FATIGUE: NON-PHARMACOLOGICAL INTERVENTIONS

- PHYSICAL ACTIVITY
- PSYCHOSOCIAL INTERVENTIONS
- MIND-BODY INTERVENTIONS
  - ginseng
  - yoga
  - acupuncture
  - massage
  - music therapy
PHYSICAL ACTIVITY

- Initiating/maintaining adequate levels of physical activity can reduce cancer-related fatigue in post-treatment survivors.

- Actively encourage all patients to engage in a moderate level of physical activity after cancer treatment (e.g., 150 minutes of moderate aerobic exercise, such as fast walking, cycling, or swimming, per week with an additional 2 to 3 sessions per week of strength training such as weight lifting unless contraindicated).

- Walking programs are generally safe for most cancer survivors and cancer survivors can begin this program after consulting with their doctors, but without any formal exercise testing such as a stress test.
PHYSICAL ACTIVITY

- Survivors at higher risk of injury (e.g., those living with neuropathy, cardiomiopathy, or other long-term effects of therapy other than comorbidities) should be referred to a physical therapist or exercise specialist.

- Breast cancer survivors with lymphedema should also consider meeting with an exercise specialist before initiating upper body strength-training.

- Common barriers to physical activity in cancer survivors include physical and disease-related limitations (e.g., pain, weakness) as well as lack of time, lack of interest/motivation, lack of facilities and lack of encouragement from family.
PSYCHOSOCIAL INTERVENTIONS

- Cognitive behavioral therapy/behavioral therapy can reduce cancer-related fatigue in post-treatment survivors

- Psychoeducational therapies/educational therapies can reduce cancer-related fatigue in post-treatment survivors

- Can be provided in the form of a group therapy as part of rehabilitation programmes or individually
MIND-BODY INTERVENTIONS: GINSENG  
(Barton D et al. JNCI 2013; 105: 1230-38)

- A double-blind trial randomized 364 fatigued cancer survivors to 2000 mg of American ginseng vs placebo (two doses at day) for 8 weeks.

- A statistically significant difference was seen at 8 weeks with a change score of 20 for the ginseng group and 10.3 for the placebo (Multidimensional Fatigue Symptom Inventory).

- Toxicity did not differ statistically significantly between the two arms.
MIND-BODY INTERVENTIONS: YOGA

- A systematic review of randomized controlled trials evaluating the effect of yoga interventions on self-reported fatigue in cancer patients and survivors has been published.

- Ten articles met inclusion criteria: a total of 583 participants who were predominantly female, breast cancer survivors have been included.

- Four studies indicated that the yoga intervention resulted in significant reductions in self-reported fatigue from pre to post-intervention.
MIND-BODY INTERVENTIONS: YOGA

- Conclusions should be interpreted with caution because risk of bias was high (inconsistent methods used across studies, etc.)

- More well-planned randomized studies are needed to determine the impact of yoga intervention on fatigue in cancer pts and survivors
MIND-BODY INTERVENTIONS: ACUPUNCTURE

- A systematic review of randomized clinical trials evaluating the role of acupuncture (AT) or electroacupuncture (EA) for manage of cancer related fatigue has been carried out

- Seven RCTs met the eligibility criteria. Most were small pilot studies with serious methodological flaws. Four studies showed effectiveness of AT or AT in addition to usual care over sham AT, usual care, or no intervention for alleviating fatigue. Three RCT showed no effect AT/EA over sham treatment
MIND-BODY INTERVENTIONS: ACUPUNCTURE

- The quantity and the quality of RCTs included in this analysis were too low to draw meaningful conclusions. Even in the positive trials it remained unclear whether the observed outcome was due to specific effects of AT/EA or nonspecific effects of care.

- Further research is required to investigate if AT/EA demonstrates specific effects on cancer-related fatigue
The following interventions may offer some benefit; however, additional research, particularly in the post-treatment population, is needed:

- Biofield therapies (touch therapy)
- massage
- music therapy
- relaxation
- moxibustion (applies the heat of burning herbs on the skin)
- reiki
- qigong (traditional Chinese energy exercises and therapies)