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Sequential multiple-assignment randomized trial design of neurobehavioral treatment for patients with metastatic malignant melanoma undergoing high-dose interferon-alpha therapy

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Abstract

Background—Interferon-alpha therapy, which is used to treat metastatic malignant melanoma, can cause patients to develop two distinct neurobehavioral symptom complexes: a mood syndrome and a neurovegetative syndrome. Interferon-alpha effects on serotonin metabolism appear to contribute to the mood and anxiety syndrome, while the neurovegetative syndrome appears to be related to interferon-alpha effects on dopamine.

Purpose—Our goal is to propose a design for utilizing a sequential, multiple assignment, randomized trial design for patients with malignant melanoma to test the relative efficacy of drugs that target serotonin versus dopamine metabolism during 4 weeks of intravenous, then 8 weeks of subcutaneous, interferon-alpha therapy.

Methods—Patients will be offered participation in a double-blinded, randomized, controlled, 14-week trial involving two treatment phases. During the first month of intravenous interferon-alpha therapy, we will test the hypotheses that escitalopram will be more effective in reducing depressed mood, anxiety, and irritability, whereas methylphenidate will be more effective in diminishing interferon-alpha-induced neurovegetative symptoms, such as fatigue and psychomotor slowing. During the next 8 weeks of subcutaneous interferon therapy, participants whose symptoms do not improve significantly will be randomized to the alternate agent alone versus escitalopram and methylphenidate together.

Results—We present a prototype for a single-center, sequential, multiple assignment, randomized trial, which seeks to determine the efficacy of sequenced and targeted treatment for the two distinct symptom complexes suffered by patients treated with interferon-alpha.

Limitations—Because we cannot completely control for external factors, a relevant question is whether or not ‘short-term’ neuropsychiatric interventions can increase the number of interferon-alpha doses tolerated and improve long-term survival.

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Conclusions—This sequential, multiple assignment, randomized trial proposes a framework for developing optimal treatment strategies; however, additional studies are needed to determine the best strategy for treating or preventing neurobehavioral symptoms induced by the immunotherapy interferon-alpha.

Introduction

Major depressive disorder (MDD), a common central nervous system disorder affecting medically ill patients, is characterized by one or more episodes of depressed mood or loss of interest lasting at least 2 weeks, with changes in appetite, weight, sleep, energy, or psychomotor activity; feelings of guilt or worthlessness; difficulty thinking or concentrating; and/or suicidal ideation [1]. Depression in the medically ill is associated with reduced treatment adherence, impaired quality of life, increased morbidity, and increased mortality [2]. Though reported prevalence rates vary due to differences in definitions and measures of depression in the medically ill [2], depressive symptoms develop in at least 25–35% of cancer patients [3].

Chronic stress on the hypothalamic-pituitary-adrenal (HPA) axis increases vulnerability to the development of MDD in individuals with cancer [4]. Activation of innate immune responses and release of cytokines in cancer patients may contribute to development of neuropsychiatric disorders [5,6], especially in individuals undergoing cancer treatments using supraphysiologic concentrations of cytokines [7]. Increasing data suggest that Interferon (IFN)-alpha effects on serotonin (5HT) metabolism contribute to the mood syndrome, while the neurovegetative syndrome may be related to IFN-alpha effects on dopamine (DA) [8].

Relevant in this regard, pretreatment with the selective serotonin reuptake inhibitor (SSRI) antidepressant, paroxetine, was shown to significantly reduce the development of depression and increase treatment adherence in malignant melanoma patients undergoing high-dose IFN-alpha therapy [9]. In a randomized, placebo-controlled study, fluoxetine, an SSRI antidepressant, improved overall quality of life by reducing depressive symptoms in cancer patients with advanced solid tumors [3]. While these and other traditional efficacy, or randomized controlled, trials demonstrate the benefits of antidepressant therapy in cancer patients [10,11], subsequent courses of action remain unclear when single antidepressant therapies fail.

Advances in clinical trial and statistical methodologies have set the stage for more sophisticated trial designs, such as sequential, multiple assignment, randomized trials (SMART) [12,13] that investigate the efficacy of sequenced treatments for patients with serious, chronic medical disorders who suffer from comorbid neuropsychiatric disorders [12,14,15]. Sorely needed is a randomized, sequenced trial evaluating multi-phase treatments to minimize neurobehavioral symptoms, improve compliance to antineoplastic therapy, and improve the quality of life in patients with cancer. Through characterization of sequenced antidepressant therapy for patients with cancer and comorbid depression, long-term care of these individuals could be optimized. We propose a two-phase, SMART in patients with malignant melanoma to evaluate the efficacy of different neurobehavioral treatments in reducing mood complex and neurovegetative symptoms and maximize adherence to IFN-alpha treatment.

Methods

Study participant recruitment

One hundred potential study participants with completely resected T4 Stage III or IV malignant melanoma at a single clinical center who will receive IFN-alpha treatment will be screened for eligibility (Table 1), and offered participation in the two-phase, SMART (Phase I: escitalopram or methylphenidate (MPH) 2 weeks prior to and 4 weeks after initiation of IFN-alpha treatment, followed by Phase II: 8 weeks of escitalopram versus MPH versus escitalopram + MPH) (Figure 1).

Most IFN-alpha treatment-eligible patients are in an adjuvant setting with history of prior surgery, but no systemic therapy; therefore, prior treatments for malignant melanoma will be noted, but will not affect eligibility for this proposed SMART study. As patients will undergo stratified randomization to two 'active' therapies by current depression status, patients who fulfill DSM-IV criteria for MDD at screening may enter the study.

We expect a refusal rate of 25% after screening, resulting in 75 patients recruited and a final number of 70 patients evaluated, considering drop-outs or study discontinuation (~35 patients per initial randomization group in Phase I) for statistical analysis. This study design results in six groups of patients at the end of Phase II, which follow four treatment strategies (Table 2).

Primary endpoint of interest

The primary endpoint will determine which of the four treatment strategies (Table 2) maximizes adherence to 12 weeks of IFN-alpha treatment, as determined by the number of IFN-alpha treatments tolerated and study drop-out rate due to all causes. By considering the effect of initial treatment with MPH to address the neurovegetative syndrome followed by augmenting with escitalopram to reduce the mood complex (Strategy c), it can be determined whether treating the neurobehavioral symptoms in this manner will most effectively maximize adherence to IFN-alpha treatment.

Other endpoints of interest

Secondary endpoints will determine whether initial treatment with an SSRI, escitalopram (Strategies a and b), will more significantly reduce mood symptoms (depression, anxiety, and irritability), while initial treatment with a DA and norepinephrine reuptake inhibitor (DNRI), MPH (Strategies c and d), will more significantly reduce neurovegetative symptoms (fatigue, anorexia, altered sleep, and psychomotor slowing), thus improving adherence to weeks of IFN-alpha therapy [16]. This effect should be most marked during Phase I of treatment. Evaluation of mood symptoms will depend on Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) [17] scores, Zung Depression Rating Scale (Zung) [18] scores, and side effect profile. Evaluation of neurovegetative symptoms will depend on the HAM-D, Neurotoxicity Rating Scale (NRS) [19], and side effect profile. Both Phase I treatment groups will be evaluated for adherence to IFN-alpha therapy. Since most secondary outcomes are measured repeatedly over time, the area under the curve will be the cumulative measure of the symptoms and toxicity.

Tertiary endpoints will determine whether the switch or augment choice is preferable for 'nonremitters' of Phase I. This will be evaluated using the cumulative measures of IFN-alpha treatment adherence (Table 3). We hypothesize that the 'augment' option during Phase II is more optimal for improving IFN-alpha adherence in 'nonremitters.' This is a clinically important question, as subjects randomized to the combined escitalopram + MPH regimen

may experience more adverse effects given their ingestion of two (rather than one) psychotropic study medications.

Intervention and study protocol schedule

Randomized study medication (escitalopram or MPH) treatment will begin 2 weeks prior to and continue during the initial 4 weeks of 20 million U/m² daily intravenous (IV) IFN-alpha therapy (Phase I). At the end of Phase I, prior to the initiation of the subsequent 8 weeks of 10 million U/m² thrice-weekly subcutaneous (SQ) IFN-alpha therapy for Phase II, participants will be evaluated to determine whether or not they experienced remission of neurobehavioral symptoms. Participants will continue with their initial agent if their HAM-D score is ≤ 11 after 4 weeks of IV IFN-alpha therapy. If their HAM-D is >11 , study participants will undergo a second randomization and either: (a) be 'switched' to the alternative agent alone, or (b) have their initial agent 'augmented' with the alternative agent for the remainder of Phase II.

In both Phase I and II, participants undergo treatment for 6–8 weeks, as our previous study showed that antidepressant prophylactic response begins at 4 weeks of IFN-alpha therapy [9]. Progression to Phase II of treatment after 6 weeks of Phase I treatment is justified, as lack of response to treatment at 6 weeks warrants modification of the treatment strategy to prevent prolonging a suboptimal treatment strategy. Furthermore, as study participation adherence is facilitated by minimizing additional visits for evaluation, completing a comprehensive evaluation of psychiatric status at the same point as transitioning a patient from IV to SQ IFN-alpha therapy would minimize patient burden.

The screening visit will occur 2 weeks prior to initiation of IFN-alpha therapy; all other study visits will occur during inpatient or outpatient treatment at the beginning of each week during the first month of IV IFN-alpha therapy (Visits 1, 2, 3, 4 at Weeks 1, 2, 3, 4, respectively), and the beginning of each month of SQ IFN-alpha therapy (Visits 5, 6, and the post-treatment follow-up visits at Weeks 8, 12, and 16 since initiation of IFN-alpha, respectively). During the first month of IV IFN-alpha treatment, the daily dose of IFN-alpha is greater and requires closer monitoring of patients' adverse events than the 8 weeks during which patients will have SQ thrice-weekly therapy of a lower dose of IFN-alpha.

Neuropsychiatric symptoms will be evaluated by psychiatrically trained raters using the Structured Clinical Interview for DSM-IV (SCID) [20], the observer-rated semi-structured interviews, the HAM-D, HAM-A, and the Clinical Global Improvement (CGI) [21] standardized assessments. At each visit, participants will complete the dimensional self-report instruments, the Zung and NRS. Input regarding participants' neurobehavioral symptoms will be elicited from a member of the patient's support system. In addition, adverse events, prescribed concomitant medications, compliance with study medication (number of pills taken), and the number of doses of IFN-alpha administered will be recorded.

Special issues: maintenance of treatment blinding

To maintain blinding with regard to study medication identity, research personnel who are not involved in study medication administration and management will evaluate patients' neurobehavioral symptoms from visit to visit. The research psychiatrist will rate the patient at the screening visit and at the end of Phase I, administer study medications, query participants with regard to side effects, and determine whether the patient will maintain his/her study medication or undergo a second randomization at the end of Phase I.

At the beginning of Phase II, though the identity of the study medication will remain concealed, raters and patients alike will become aware of which patients are 'remitters'

versus ‘nonremitters.’ Any positive effect of revealing response status may be a benefit of an adaptive treatment strategy; this is an integral component of sequenced treatment that likely improves patient compliance. Regardless of remission status and treatment arm in Phase II, patients will undergo identical ingestion of study medication from two bottles and placebo/medication taper to maintain similar patient burden of ingesting multiple medications.

Randomization and treatment of depressive symptoms during phase I

During the first 6 weeks of Phase I (2 weeks before IFN-alpha treatment and 4 weeks during IV IFN-alpha treatment), escitalopram or MPH will be administered as a single agent. After an initial screening visit 2 weeks prior to initiating IFN-alpha therapy, subjects will be randomized to treatment groups that are stratified according to MDD status at screening. During the first week, they will begin with ingesting one tablet a day (10 mg of escitalopram or MPH). Double-blind study medication for each patient will be packaged individually and code-labeled with a randomization package number. Packaging, size, and color of tablets will be the same regardless of treatment group. During the second week, study medication can be increased up to two tablets per day, as tolerated (20 mg of escitalopram or MPH per day). In all cases, study medication dosage will be individually adjusted to achieve maximum clinical therapeutic effect.

Each patient’s psychiatric status will be closely monitored on a weekly basis during initial IFN-alpha IV therapy. Those who experience an increase in HAM-D scores that lead to a 1 point increase in CGI and do not return to the level of their baseline screening visit will be monitored on a weekly basis or as needed to assess the need for additional treatment and/or study discontinuation (see ‘Discontinuation during Phase I or II’). Treatment with the initial study medication (escitalopram or MPH) will continue for 6 weeks, the minimum recommended treatment duration for assessment of an antidepressant’s efficacy for a patient with MDD [22,23].

The second randomization at the end of phase I and maintenance of the double-blind during phase II

At week 6 (Visit 5), participants will be reevaluated to determine response to treatment or possible remission status, and will enter Phase II of the trial. Participants with HAM-D scores ≥ 11 (i.e., ‘remitters’) will remain on their original study medication during the remaining 8 weeks of the study. They will be given study medication Bottle #1 (containing their original study medication of either two tablets of escitalopram 10 mg or MPH 10 mg) and Bottle #2 (containing placebo) to maintain equal demands on patients for treatment adherence. Study subjects will be instructed to ingest at least one tablet each daily from Bottle #1 and #2 during Phase II of the trial. As Table 4 shows, ‘remitters’ will receive a ‘taper bottle’ (Bottle #3) of placebo tablets and be instructed to ingest one tablet daily for 7 days, and then discontinue, providing consistency with the tapering process of ‘nonremitters’ who undergo a switch in Phase II.

Subjects with HAM-D scores ≥ 12 at week 6 who originally received escitalopram will receive: (a) Bottle #1 containing escitalopram + Bottle #2 containing MPH, or (b) Bottle #1 containing MPH + Bottle #2 containing placebo. The rationale for augmenting escitalopram with MPH during Phase II, as in Strategy a, is that the combined pharmacologic effects upon 5HT and DA central nervous system pathways may be more beneficial in ameliorating the neurovegetative syndrome than targeting a single pathway alone. The rationale for Strategy b, switching to MPH alone, is that the amelioration of the neurovegetative syndrome and associated tolerability of a single DNRI agent may more significantly improve compliance during SQ IFN-alpha therapy. As there is no clear evidence that either augmentation of an

antidepressant or switching to another antidepressant treatment regime is a superior choice [24], we elected to have equal randomization for Phase II.

Subjects with HAM-D scores ≥ 12 at week 6 (i.e., ‘nonremitters’) who received MPH originally will receive: (c) Bottle #1 containing MPH + Bottle #2 containing escitalopram, or (d) Bottle #1 containing escitalopram + Bottle #2 containing placebo. The rationale for augmenting escitalopram with MPH during Phase II, as in Strategy c is identical to the rationale of Strategy a above. The rationale for Strategy d, switching to escitalopram alone, is that the amelioration of the mood and anxiety syndrome and associated tolerability of a single SSRI agent may be the superior treatment option with regards to compliance during SQ IFN- α therapy.

Study participants randomized to all strategies will be advised to begin their study medication at one tablet daily for 7 days, and then increase to two tablets daily, as tolerated for the remainder of Phase II. Study participants randomized to all strategies will receive a ‘taper bottle’ (Bottle #3) of escitalopram (for Strategy b), MPH (for Strategy d), or placebo (for Strategies a and c) for the first week of Phase II, in which they will ingest one tablet of study medication daily for 7 days, and then discontinue. This will act to minimize any withdrawal symptoms from discontinuing escitalopram and MPH in patients undergoing therapy under Strategies b and d, respectively.

Discontinuation during phase I or II

The psychiatrist will determine whether patients can continue participation. Patients who are discontinued from the study (see Table 5) will be evaluated in a termination post-treatment visit and classified as ‘remitters’ or ‘nonremitters.’ At the discretion of the psychiatrist, these patients can receive open-label MPH or open-label escitalopram for 3 months after their SMART termination. If possible, all discontinued patients will be reevaluated on the same visit schedule as they would if they were enrolled in the study. This will allow an intent-to-treat analysis to be conducted. Participation in these evaluations or in the open-label treatment phase is voluntary for all patients. All patients will be informed of available mental health resources and assisted with psychiatric referral, as needed, after their study participation has ended.

Statistical analyses

Analysis of phase I: intermediate outcomes—Because Phase I is a randomized comparison of two treatments, usual statistical analysis (i.e., two sample *t*-tests) can be conducted for the intermediate outcomes measured in Phase I. Survival analysis will be used for the time-to-event outcome (time to drop-out, development of HAM-D score ≥ 18 , and development of toxicity requiring IFN- α treatment discontinuation). Generalized Estimating Equation (GEE) models will be used to assess the treatment effects for repeatedly measured outcomes, including the number of IFN- α treatments tolerated as well as secondary outcomes (scores on the HAM-D, HAM-A, Zung, NRS, and CGI). These analyses will be adjusted for individual risk factors, such as family history of depression, age, gender, early life adversity, and socioeconomic status. For GEE models, Akaike’s information criterion [25] will be used to measure the goodness of fit of the resulting statistical models, which will allow us to select the ‘best’ treatment model. In the presence of missing data, we will use the inverse-weighted methods based on the estimated probabilities of being missing [26,27].

Analysis of phase I and II: final outcomes—We will perform statistical analyses to evaluate the delayed treatment effects after completion of both phases of the SMART. As outlined in Table 3, Questions of interest include: (1) Which of the four strategies (Table 2)

is optimal for maximizing adherence to IFN-alpha therapy; (2) which initial treatment (escitalopram vs. MPH) optimally increases IFN-alpha treatment adherence by minimizing neurobehavioral symptoms; and (3) of the switch and augment Phase II strategies, which is more efficacious for increasing IFN-alpha treatment adherence in Phase I ‘nonremitters’?

Question 1 requires the estimation of the mean outcome under a dynamic treatment regime [28,29] using marginal mean models [29]. We will choose the treatment strategy with the best mean outcome (i.e., adherence to IFN-alpha treatment) as the optimal strategy without using hypothesis testing. There are two reasons behind our choice of such an approach. First, for the purpose of comparing sequenced treatment strategies, our trial is intended to be exploratory, not confirmatory. Hence, much like typical phase II clinical trials, it is reasonable to just ‘pick the winner’ rather than conduct hypothesis testing [30]. Our findings will be combined with results from other exploratory trials to screen for the most promising strategies and generate specific hypotheses, which subsequently can be tested in standard randomized confirmatory trials. Second, when hypothesis testing is used to compare four treatment strategies, multiple comparison adjustments need to be used, and considerably larger sample sizes are needed, which is often not feasible for hypothesis generating trials.

To answer Question 2, we will divide the study population into two groups: one treated by strategies that start with escitalopram and the other treated by strategies that start with MPH. Because patients are randomized into these two groups at the beginning of Phase I, these two groups are comparable and the mean outcomes of interest (i.e., IFN-alpha therapy compliance, severity of mood symptoms, and severity of neurovegetative symptoms) can be compared using two sample *t*-tests.

To answer Question 3, we will divide Phase I ‘nonremitters’ into two groups: one assigned to the switch strategy, and the other assigned to the augmenting strategy. Due to the randomization at the start of both Phase I and II, these groups are comparable, and standard statistical analyses (i.e., two sample *t*-tests) can be conducted to choose the better strategy for maximizing IFN-alpha treatment adherence. In addition, analyses similar to those proposed for evaluation of Phase I intermediate outcomes will be conducted for Questions 2 and 3.

Power considerations—We expect to have a total of $n = 70$ patients with complete records. Using a simulation approach [31], it is shown that an equal randomization probability in Phase I and II will maximize the chances of choosing the true optimal strategy [28] for Question 1. For $n = 70$, the simulation shows that the probability of correctly choosing the optimal strategy is >80% when standardized effect size (defined as the mean difference divided by the standard deviation) between the two best strategy means is 0.46. An equal randomization probability in both phases maximizes the power for other planned statistical analysis. When two-sample *t*-tests are used, our study will achieve 80% power to detect a standardized effect size of 0.68 for the analysis of Questions 1 and 2. The power of study for Question 3 depends on the rate of remission after Phase I, which alters the sample size entering the switch and augment arms in Phase II. When the rate of remission is low, at 10%, the minimal detectable standardized effect size is 0.72; when it is high, at 40%, the minimal detectable standardized effect size is 0.89. Overall, a sample size of $n = 70$ will achieve adequate power to test most of the questions of interest, and generate scientific hypotheses for future confirmatory trials.

Although SMART trials can randomize ‘remitters’ to examine the effect of a sequence of treatments for ‘remitters’, we chose not to randomize ‘remitters’ to minimize the risks of depressive symptom development. By not randomizing ‘remitters,’ our proposed SMART study gains power, specifically, if $n/2$ is the sample size in each of the group of Phase I and

p is the response rate to Phase I. Then, there are $np/2$ Phase I ‘remitters’ and $n(1-p)/2$ Phase I ‘nonremitters’; 50% of ‘nonremitters’ ($n(1-p)/4$) will be assigned to one of two Phase II strategies. Since each strategy of interest includes the treatment option for both ‘nonremitters’ and ‘remitters,’ the number of subjects that follow a specific treatment strategy is the sum of the ‘remitters’ ($np/2$) and ‘nonremitters’ ($n(1-p)/4$) that follow this strategy, that is $\frac{1}{4} + (\frac{1}{4})p$. This allows the remitters to be shared by two strategy groups, hence improving power. Alternatively, if the ‘remitters’ are randomized to two treatment options with equal probabilities, only $(\frac{1}{4})n$ subjects will follow a specific treatment strategy.

Discussion

Justification for treatment strategies

Various cytokines influence monoamine metabolism to alter the 5HT, DA, and norepinephrine systems [32]. Administration of exogenous cytokines, as in with IFN-alpha therapy, alters the endogenous monoamine systems thus contributing to the development of depressive symptoms associated with downregulation of 5HT and neurovegetative symptoms associated with downregulation of DA [33].

To compensate for the alteration to the monoamine systems due to administration of supraphysiologic concentrations of cytokines with IFN-alpha therapy, we propose that we use an SSRI, escitalopram, to address mood complex syndrome associated the serotonergic system. Among the SSRIs, escitalopram is shown to be the safest when used in its recommended dose of 10–20 mg, with minimal drug interactions [34] and mild, mostly transient, side effects [34,35].

To address neurovegetative symptoms associated with the DA and norepinephrine systems, we elected to use a DNRI, MPH. MPH is a psychostimulant and not typically used as a stand-alone antidepressant therapy; however, it is one of many stimulants used as an augmenting therapy for treatment of depression [24]. In addition, it is shown to be effective in reducing cancer-related fatigue in an average of 20 mg doses [36], as supported by smaller-scale studies [37]. An additional review shows that MPH can be used in cancer patients to improve cognitive function and reduce opioid-induced somnolence, while augmenting their analgesic effects [38].

Together, the mechanisms of action of escitalopram and MPH may aid in restoring balance in monoamine pathways. Although evidence of its synergy in the treatment of depression requires further study, it is a safe combination therapy [39]. The effects of escitalopram and MPH treatments for depression in the cancer population have not been systematically evaluated [40], but both therapies have potential for improving overall patient outcome in our unique cancer population [41]. Addressing cancer-related fatigue with MPH prior to administration of escitalopram or during the 2 week induction period may help to improve overall patient outcome.

SMART design considerations

For our proposed study, the use of the SMART design is preferred over using a simple randomized control trial for various reasons. SMART designs are beneficial in addressing multiple concerns and hypotheses. In addition to comparing the efficacy of escitalopram versus MPH versus escitalopram + MPH, this proposed SMART affords the advantage of providing insight into possible sequencing of antidepressant therapy for malignant melanoma patients undergoing IFN-alpha therapy. As development of neurobehavioral symptoms may compromise an individual’s ability to adhere to IFN-alpha therapy, characterizing a sequenced treatment response is critical. While SSRIs are a mainstay for treatment of depression [34], the rapid onset of the effects of MPH and its positive effects in

the cancer patient population [36,37] make both treatments viable options for the study population. When one treatment proves ineffective, it is difficult to determine whether attempting to address neurovegetative symptoms, mood complex symptoms, or beginning augmentation therapy using escitalopram and MPH in this specific patient population would maximize tolerance to IFN-alpha therapy. SMART designs allow for clear characterization of synergistic effects in sequenced therapies [42]; thus, we could characterize the use of escitalopram and MPH as a combination therapy in patients with malignant melanoma undergoing IFN-alpha therapy. By using the SMART design, we can address the complexities in both treatment choice and sequencing, as well as any interactions that may occur due to synergistic effects of the therapies in question.

The second randomization built into a SMART design is an additional strength. In our previous study, a lack of response to initial antidepressant treatment decreased IFN-alpha therapy compliance [9]. With a SMART design, the second randomization would allow for 'nonremitters' to receive additional treatment and care as a 'rescue option' as well as additional long-term follow up with the psychiatric team. In addition, those who experienced intolerable side effects to initial treatment would have the chance to receive alternative treatment. This level of response to patient needs would provide a benefit to the patient population.

A SMART design can be used to study both the intermediate and delayed effects of treatment associated with the sequencing process [28]. While one treatment may produce the best intermediate outcome in Phase I, the alternative treatment may produce a better long term outcome upon completion of both Phase I and II. Although MPH may immediately address neurovegetative symptoms that are recorded, the second randomization is based on overall HAM-D score, which incorporates elements of depressive symptoms that may be better addressed by the later-acting escitalopram arm. This effect is minimized by the initial 2 weeks of study medication administration prior to initiation of IFN-alpha therapy, but the slight discrepancy in duration of effect will need to be considered through interpretation of the study findings.

Additionally, our study only uses one tailoring variable (HAM-D) and one decision rule (>11), focused primarily on cumulative neurobehavioral symptoms rather than mood complex or neurovegetative symptoms alone, to decide the treatment strategy during Phase II; however, many other variables that may be used to determine the treatment sequences are collected in this study. As some patients may be resilient to the development of neurovegetative symptoms, yet derive some benefit from escitalopram in the (expected) amelioration of their anxiety and mood symptoms during Phase I of IFN-alpha therapy, we decided to use total HAM-D symptom score at the randomization points to incorporate a balance of patient benefits and study focus. Nevertheless, as a very attractive feature of the SMART design, we can use the observed data to estimate the optimal strategy among more complicated treatment sequences, which may include additional tailoring variables and decision rules. For example, we can test whether adherence to IFN-alpha treatment is a good alternative or additional tailoring variable and determine the optimal decision rule using semi-parametric methods [43,44] and parametric learning methods such as Q-Learning [45].

While SMARTs provide insight into development of a sequenced treatment strategy, standard randomized trials are needed to confirm the true efficacy of the strategy as well as characterize interactions between and subtle effects of consecutive sequenced treatment choices. Future studies will be needed to optimize and refine elements of the treatment strategy, such as treatment duration and dosage.

Additional study limitations

A relevant critical question is whether ‘short-term’ neuropsychiatric intervention (e.g., 14 weeks of antidepressant treatment) to ameliorate IFN-alpha-induced neurobehavioral symptoms, and potentially improve tolerance of IFN-alpha therapy, can improve long-term survival. A much larger sample of subjects, possibly through a multi-center study, would be required to test such a hypothesis. Treatment adherence (i.e., number of IFN-alpha doses received) may serve as a reasonable surrogate variable, and the 5-year survival of this study’s participants can be examined. Relevant in this regard, the study will not be negatively influenced by patients who discontinue IFN-alpha therapy prior to the end of the study, and treatment discontinuations in MPH-treated versus escitalopram-treated patients as well as intent-to-treat analysis are of great interest.

As described in ‘SMART design considerations’, our study can be used to estimate the optimal treatment strategy from complicated treatment sequences that include additional tailoring variables and decision rules. However, in this analysis, one will need to deal with nonregular parameters, which has been noted [44] as potentially causing bias in parameter estimation and leading to inadequate coverage of their confidence intervals. While attempts have been made to correct the bias and improve coverage properties [46,47], statistical methods that perform well under a wide range of settings have yet to be developed.

Conclusion

Our prototype trial is designed to inform the construction of a sequenced treatment strategy. While the proposed SMART is a starting point for developing one possible effective sequenced treatment strategy to address IFN-alpha-induced neurobehavioral symptoms, it is limited in its scope of testing only escitalopram, MPH, and escitalopram + MPH combination therapies. Behavioral therapies and other common augmentation therapies would need to be evaluated in future studies to thoroughly address the needs of the study population. Moreover, additional trials to refine the strategy for the treatment of depression in patients with malignant melanoma receiving high-dose IFN-alpha therapy might also include other neurobehavioral interventions. Construction of SMART strategies offers the potential to alleviate the suffering of cancer patients with neurobehavioral symptoms, which adversely affect quality of life and interfere with potentially life-saving therapies.

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Glossary

5HT	Serotonin
CGI	Clinical Global Improvement
DA	Dopamine
DNRI	Dopamine and Norepinephrine Reuptake Inhibitor
GEE	Generalized Estimating Equation
HAM-A	Hamilton Anxiety Rating Scale

HAM-D	Hamilton Depression Rating Scale
HPA	Hypothalamic-Pituitary-Adrenal
IFN	Interferon
MDD	Major Depressive Disorder
MPH	Methylphenidate
NRS	Neurotoxicity Rating Scale
SSRI	Selective Serotonin Reuptake Inhibitor
SMART	Sequential Multiple Assignment Randomized Trial
SCID	Structured Clinical Interview for DSM-IV
Zung	Zung Depression Rating Scale

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Figure 1.

Phase I (weeks 0–6) and Phase II (weeks 6–14) of SMART of patients with malignant melanoma undergoing IFN-alpha therapy

Table 1

Study population inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Age 18 years old • Able to provide informed consent (self or legal representative) • Individuals with completely resected Stage T4, III, IV malignant melanoma with no major cardiac, pulmonary, renal disease or cancers • Eligible and anticipated to receive IFN-α treatment 	<ul style="list-style-type: none"> • Individuals undergoing effective antidepressants or other psychopharmacologic therapies • Individuals with conditions that could affect central nervous system function (e.g., brain metastases, history of brain injury, seizure disorders) • Individuals with conditions that could affect compliance to the study (e.g., ongoing alcohol or substance abuse, disabling personality disorder) • History of suicide attempt, psychotic symptoms, or psychiatric hospitalization in prior 12 months • Evidence of untreated or poorly controlled infectious, endocrine, cardiovascular, hematological, renal, or neurological disease • Prior history of severe adverse events associated with escitalopram (or other SSRI antidepressants) or methylphenidate

Table 2

Different treatment strategies for symptom ‘remitters’ and symptom ‘nonremitters’ of patients with malignant melanoma receiving IFN- α

Strategy	Pathway for symptom ‘remitters’ Phase I	Phase II	Pathway for symptom ‘nonremitters’ Phase I	Phase II
1	Escitalopram	Escitalopram	Escitalopram	Augment (escitalopram + MPH) (Strategy a)
2			Escitalopram	Switch (to MPH) (Strategy b)
3	MPH	MPH	MPH	Augment (escitalopram + MPH) (Strategy c)
4			MPH	Switch (to escitalopram) (Strategy d)

Table 3**Study endpoints**

Primary endpoint is to compare which of the four treatment strategies in malignant melanoma patients undergoing IFN-alpha therapy is most effective in maximizing adherence to 12 weeks of IFN-alpha treatment.

- The number of IFN-alpha treatments tolerated for individual patients in each treatment group
- The overall study drop-out rate due to all causes in each treatment group

Question: Which of the four treatment strategies (escitalopram augmented with MPH, escitalopram switched to MPH, MPH augmented with escitalopram, MPH switch to escitalopram) is optimal for maximizing adherence to IFN-alpha therapy?

Secondary endpoints are to determine whether initial treatments (escitalopram or MPH) will each target their own aspect of the neurobehavioral symptoms that develop as a result of IFN-alpha therapy.

- The number of IFN-alpha treatments tolerated for individual patients in each Phase I treatment group
- The overall study drop-out rate due to all causes in each Phase I treatment group
- Symptoms of depressed mood, anxiety, and irritability measured by HAM-D, HAM-A, and Zung in patient groups initially treated with escitalopram and initially treated with MPH
- Symptoms of fatigue, anorexia, altered sleep, and psychomotor slowing measured by HAM-D and NRS in patient groups initially treated with escitalopram and initially treated with MPH

Question: Which initial treatment (escitalopram vs. MPH) optimally increases IFN-alpha treatment adherence by minimizing neurobehavioral (mood complex and neurovegetative) symptoms?

Tertiary endpoints are to determine whether switch or augment is the preferable option for alleviating neurobehavioral symptoms and maximizing IFN-alpha treatment adherence in patients who do not respond to individual SSRI or DNRI therapies?

- The number of IFN-alpha treatments tolerated for individual patients undergoing switch vs augment strategy during Phase II
- The overall study drop-out rate due to all causes in patients undergoing switch vs augment strategy during Phase II

Question: Of the switch and augment Phase II strategies, which is more efficacious for increasing IFN-alpha treatment adherence in Phase I 'nonremitters'?

Table 4

Phase II treatment regimen and pill bottles

Patient classification	Treatment option	Bottle #1	Bottle #2	Bottle #3 (taper bottle with 7 tablets)
Remitter	Continue	Escitalopram	Placebo	Placebo
Remitter	Continue	MPH	Placebo	Placebo
Nonremitter (Phase I: Escitalopram treatment)	Augment Switch	Escitalopram MPH	MPH Placebo	Placebo Escitalopram
Nonremitter (Phase I: MPH treatment)	Augment Switch	MPH Escitalopram	Escitalopram Placebo	Placebo MPH

Table 5**Study discontinuation criteria**

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- The patient is unable to tolerate the full 12 weeks of IFN-alpha treatment due to
 - a. Recurrence or worsening of melanoma,
 - b. Intolerable side effects, and/or,
 - c. Development of severe neuropsychiatric symptoms.
 - The patient experiences any serious adverse events associated with ingesting escitalopram and/or MPH.
 - The patient experiences severe depression or relapses (depression worsens), as determined by the following:
 - a. the patient becomes suicidal or psychotic,
 - b. the patient's HAM-D score increases >18
 - c. over two consecutive visits, the patient's HAM-D score significantly increases so that the CGI increases by at least 1 point, and/or,
 - d. the principal investigator judges the patient's clinical condition to have significantly worsened, warranting alternative psychotropic treatment.
 - Investigators judge discontinuation to be in the patient's best interest.
 - The patient requests discontinuation from the study.
 - There is protocol violation.
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