

Original Article

Hope, quality of life and benefit from treatment in women having chemotherapy for platinum resistant/refractory recurrent ovarian cancer - the GCIG Symptom Benefit Study

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Abstract

Purpose

Chemotherapy for platinum resistant/refractory ovarian cancer is motivated by the hope of benefit. We sought to determine relationships between: a) trait hope, expectation of symptom benefit from chemotherapy, anxiety and depression; b) hope and perceived efficacy of chemotherapy; and c) dashed hope (where expectations for benefit are not fulfilled) and depression.

Methods

Adult patients enrolled within Stage 1 of the GCIG Symptom Benefit Study were included. Patient reported outcomes were collected at baseline, prior to the first 4 treatment cycles (12 – 16 weeks) and 4 weeks after completing chemotherapy or at disease progression, whichever came first in 126 women with predominantly platinum resistant ovarian cancer. Associations were assessed with Spearman's rank correlation coefficient (r) and odds ratio.

Results

Trait hope and expectation of symptom benefit from chemotherapy were weakly correlated with each other (r 0.25). Trait hope, but not expectation of symptom benefit was negatively correlated with anxiety (r -0.43) and depression (r -0.50). The smaller the discrepancy between perceived and expected symptom benefit, the less likely the patient was to have scores indicative of depression (Odds ratio 0.68: 95% CI 0.49-0.96, P = 0.026).

Conclusion

Trait hope and expectation of symptom benefit from chemotherapy appear to be distinct, and independent of aspects quality of life and scores for depression. Hope did not appear to affect perceived efficacy of chemotherapy in alleviating symptoms, but women whose expectation of symptom benefit from chemotherapy was not fulfilled were more likely to have scores indicative of depression. It may be preferable to encourage hope towards achievable goals rather than benefits from chemotherapy.

Abstract: 260

Introduction

Ovarian cancer is the leading cause of death in women with gynecological malignancies in the Western World. Most women present with advanced disease and following surgery receive platinum based chemotherapy. Although many women initially respond to treatment, the majority will unfortunately relapse within 12-18 months¹. Patients who relapse within 6 months of receiving, or during, platinum-based chemotherapy (platinum resistant /refractory) have a particularly poor prognosis, with a median survival ranging from 3-9 months²⁻⁶. Such women are usually offered 2nd or 3rd line chemotherapy with the aims of palliation and improving quality of life, with uncertain impact on overall survival.

However, there are limited data on the actual impact of palliative chemotherapy on symptoms, or quality of life. In a prospective study of 27 women with recurrent ovarian cancer offered 2nd or 3rd line chemotherapy, only 7 had objective evidence of symptom improvement⁷.

Further, women's expectations of therapy appear to be at odds with palliative aims. In the above study, despite having been told the goal of chemotherapy was palliative, 65% of women expected chemotherapy would make them live longer and 42% thought it would cure them. This discrepancy has been reported in other advanced cancers⁸. In another study of 122 women with ovarian cancer⁸, approximately two thirds of women whose disease had relapsed ranked 'tumour shrinkage' as the 'most important' goal of treatment during repeated chemotherapy, with <8% rating symptom relief as the most important aim of treatment. Discordance

between doctors' treatment intent and patients' beliefs about cure increased from 24% at first-line to 83% by fourth-line chemotherapy. Many women, while acknowledging that their disease is incurable, seemingly choose to have chemotherapy as an antidote to hopelessness, to feel they are doing something, and have done everything possible to prolong life^{9, 10}.

Some health professionals feel that maintenance of hope is a medically worthwhile outcome^{9,10}, providing meaning and direction¹¹⁻¹³ and improved coping and quality of life^{12,14-17}. However, it could also be argued that giving women "medically futile" treatment purely to maintain hope is questionable. If patients' hopes are raised and then dashed, "false" hope may increase risk of depression, and side effects can further reduce wellbeing.

Despite the common perception that hope is important, there is a lack of clarity in how the term is defined and measured¹⁸. Some measures, such as the Herth Hope Index¹⁹ portray hope as a general, multidimensional trait (trait hope). In contrast, others focus on a specific element of hope, such as hope for, or expectation of, a particular outcome (for example, symptom benefit from chemotherapy)^{20,21}. The degree to which hope is distinct from psychological morbidity (anxiety and depression) is not clear. Further research is needed to better understand the role of hope in maintaining wellbeing^{22,23}. In this study, we explored associations between hope, indices of wellbeing and perceived symptom benefits of chemotherapy.

More specifically, we explored the following hypotheses in our population:

1. Trait hope and the expectation of symptom benefit from chemotherapy are

separate concepts, and will be distinct from psychological well-being and quality of life. Thus at baseline, trait hope as measured by the Herth Hope Index will be moderately but not strongly correlated with expectation of symptom benefit, and each of these will correlate moderately but not strongly with anxiety, depression and quality of life.

2. Trait hope and expectation of symptom benefit at baseline will be associated with perceived benefit from chemotherapy and improvement in self reported symptoms (FOSI) at follow-up after adjusting for anxiety and depression.
3. Raised hope, if dashed, will leave patients vulnerable to depression. Thus disparity between expectation of symptom benefit and perceived symptom benefit from chemotherapy will be associated with increased depression (depression subscale of the HADS) at follow-up.
4. Trait hope will modify the impact of a disparity between expectation of symptom benefit and perceived benefit on depression.

Methods

This sub-study was part of a larger study of symptom benefit in patients with platinum resistant/refractory ovarian cancer (Stage 1 of the GCIG Symptom Benefit Study (SBS)). This study sought to determine the aspects of HRQL rated most severe by patients, and the most common symptoms. All patients were recruited from centres in Australia and Canada, were ≥ 18 years, and had been diagnosed with epithelial ovarian, primary peritoneal or fallopian tube cancers. They all had recurrent cancer and progressive disease (based on CA125, radiological or clinical criteria). Patients with platinum resistant /refractory ovarian cancer were eligible (the vast majority of the sample), as were those with potentially platinum sensitive disease providing they were receiving their 3rd or greater line of treatment. All

patients were required to have an ECOG PS 0-3, a life expectancy of 3 months or longer, and be able to complete questionnaires independently. Choice of chemotherapy was at the discretion of the treating physician and had to commence within 2 weeks of registration. No minimum threshold was set for symptom frequency or severity.

Data was collected at baseline, prior to every treatment cycle for 4 treatment cycles (12 – 16 weeks) and one month post completion of treatment or at disease progression, whichever came first.

Study Design

The study had a longitudinal design with patient and clinician completed measures. The schedule for patient reported outcome measures is shown in Table 1. The questionnaires of relevance to this analysis included:

1. The Herth Hope Index measures the degree to which a patient feels hope and a sense of meaning in their lives. The scale has three subscales: temporality and future, positive readiness and expectancy, and interconnectedness. High scores on the measure indicate greater hope. ¹⁹

2. The Hospital Anxiety and Depression Scale (HADS) is comprised of 14 items in 2 subscales independently measuring anxiety and depression²⁴. Subscale scores of 11 or more have been determined to be consistent with clinical anxiety or depression, with higher scores indicating higher anxiety and depression. ²⁵

3. Expectation of symptom benefit and Perceived Benefit. At baseline and before starting chemotherapy patients were asked ‘How much do you expect your symptoms to improve with chemotherapy?’ using a numeric rating scale from 0 = “none at all” to 10 = “completely” (Expected benefit). At their follow up visits, after starting chemotherapy and **prior** to objective assessment of response, patients were asked: “How much have your symptoms improved with chemotherapy?” using the same scale (Perceived Benefit). If patients indicated an improvement in symptom control, they completed one item on a 5 point Likert scale (ranging from not at all to very much so) asking whether their symptom improvement was enough to affect their overall quality of life.

4. Functional Assessment of Cancer Therapy – Ovary (FACT-O) Symptom Index (FOSI)

is comprised of the FACT-G, a 28 item self reported measure that assesses four dimensions of well-being: physical, functional, social/family and emotional well-being, plus an ovarian cancer-specific subscale ²⁶. The FOSI is a very brief (8-item) index derived from the FACT-O to measure symptom response to treatment for ovarian cancer (OC). High scores on FACT-O and FOSI indicate worse quality of life.

(TABLE 1 ABOUT HERE)

Statistical methods

Data were expressed as frequencies (percentages) for categorical variables and as means \pm SD or medians (interquartile range) for normally and non-normally distributed continuous variables, respectively. The independent samples *t*-test was used to test for a difference in two group means. The FACT-O, FACT-G and FOSI scores were linearly transformed to a scale from 0 to 100.

Spearman's rank correlation coefficient (*r*) was used to examine the strength and direction of linear relationships between patient reported measurements (Hypothesis 1). Consistent with Cohen, correlations from 0.10-0.29 were considered weak, from 0.30-0.49 moderate and 0.50 or more strong²⁷.

To assess improvement or deterioration in physical well-being, two methods were used: the change in FOSI score and the rating of perceived benefit. An increase in FOSI score of at least 10 points (10% of total scale, approximately half a standard deviation) was classified as a significant improvement²⁸. A rating of perceived benefit rating of 6 or more was classified as significant perceived improvement, with this threshold representing scores of more than 10% above the median. Patients were then categorised as having improved physical well-being or not, and as having perceived benefit or not. Relationships between trait hope, expectation of symptom benefit at baseline, and improvement in physical well being or perceived benefit at the end of treatment (Hypothesis 2) were assessed using logistic regression.

Analyses with perceived benefit as the outcome were adjusted for anxiety and depression. However adjustment was not possible in analyses predicting improved physical well being due to the small number of women experiencing improved physical well being²⁹.

In the subgroup of patients without scores indicative of depression at baseline, the disparity between expectation of symptom benefit and perceived benefit was

determined by subtracting scores for perceived benefit from hope for symptom benefit. Logistic regression was then performed to assess the relationship between that disparity and development of scores indicative of depression (Hypothesis 3). All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute). Two-sided p-values <0.05 were considered statistically significant..

Results

Characteristics and Symptom Complex at Baseline

126 patients were recruited to the study and 123 had at least 1 cycle of chemotherapy. Their characteristics are shown in Table 2. Their mean age was 62 years (range 30-89 years). The majority of patients had an ECOG performance status of 0 or 1 with 32% having a performance status of 0. Most patients had platinum resistant ovarian cancer and had received more than 2 lines of prior chemotherapy; 38% had received 3 or more lines of chemotherapy. 79% of patients reported at least one symptom at moderate or severe levels based on the Patient DATA Form³⁰.

(TABLE 2 ABOUT HERE)

Hope, depression and anxiety and quality of life.

Hope, depression, anxiety and quality of life scores at baseline and at the last follow-up assessment are shown in Table 3.

(TABLE 3 ABOUT HERE)

Expectation of symptom benefit and perceived benefit from chemotherapy

Most patients expected that their symptoms would improve with treatment; 98% ($N=121$) expected some improvement (Expected Benefit score ≥ 1) 73% ($N= 91$) expected a significant improvement (Expected Benefit score ≥ 6), with 24% of patients ($N=30$) hoping that their symptoms would completely or almost completely resolve (Expected Benefit score 9 or 10). When asked at their last assessment how much their symptoms had improved, only 1 (1%) reported complete resolution of her symptoms, but at least 38% of patients reported that their symptoms had improved significantly (perceived benefit score of 6 or more).

Correlations with hope at baseline

There was a weak correlation between Trait hope and expectation of symptom benefit from chemotherapy (0.25), suggesting that they are related but distinct constructs (Table 4). Correlations between trait hope and measures of psychological well-being and quality of life were moderate: -0.43 with anxiety, 0.5 with depression, and 0.45 with emotional well-being on the FACT-O. However there were no important correlations between expectation of symptom benefit and measures of psychological well being or quality of life (Table 4). Thus our first hypothesis was partly supported.

(TABLE 4 ABOUT HERE)

Impact of baseline hope and expectation of symptom benefit, on perceived benefit and reported improvement in symptoms at follow-up

Contrary to Hypothesis 2, trait hope was not significantly associated with reported improvement in symptoms at follow-up based on either a 10 point increase in the FOSI symptom score, or on a perceived benefit rating greater than 5 (Table 5). Of those women who completed at least one on-treatment questionnaire, 44 (38%) reported a perceived benefit score >5 and 23 (20%) reported a FOSI score that increased by at least 10 points. Expectation of symptom benefit was also not associated with symptom improvement based on FOSI.

In unadjusted analysis expectation of symptom benefit was associated with a higher likelihood of a perceived benefit rating greater than 5 (Odds Ratio: 1.25 95% CI (1.03-1.52); $P = 0.022$), however after adjustment for anxiety and depression the effect was attenuated and no longer significant (Table 5).

Impact of disparity between expectation of symptom benefit and perceived benefit on development of depression

Fourteen women had scores indicative of clinical depression at baseline. Of the 111 women without scores indicative of depression at baseline, 61 completed baseline and end of treatment (or last follow up) ratings of depression, expectation of symptom benefit, and perceived benefit. 39 of these 61 reported a perceived benefit less than their expected symptomatic benefit at baseline and were included in the following analysis to test Hypothesis 3.

As hypothesised, the difference between expectation of symptom benefit and perceived benefit was significantly associated with follow-up scores indicative of depression; the greater the discrepancy between perceived benefit and expected symptom benefit, the greater the likelihood of a follow-up score indicative of depression (Odds ratio 0.68, 95% CI 0.49-0.96, $P = 0.026$). The mean difference

between expectation of symptom benefit and perceived benefit ratings among the 6 patients with scores indicative of depression was -6.8 (95% CI -9.6 to -4.1) compared to -3.8 (95% CI -4.7 to -2.8) for the 33 patients who did not have scores indicative of depression (Difference in means test: $P = 0.012$). Thus hypothesis 3 was supported, although should be interpreted cautiously given the small number of events.

Role of trait hope in mitigating the impact of dashed expectations.

Of the 39 evaluable patients who did not perceive a benefit from chemotherapy, 6 had scores indicative of clinical depression at last follow up. This number of events was insufficient to test for effect modification by levels of trait hope at baseline (Hypothesis 4).

Discussion

Our results support the distinction between general trait hope and specific expectation of symptom benefit from chemotherapy in women receiving palliative chemotherapy for platinum resistant/refractory ovarian cancer. Both hope constructs were independent of aspects of psychological well being and quality of life. Contrary to our hypotheses, patients' expectations at the beginning of treatment did not affect their perception of benefit from treatment. Importantly, if there was a large discrepancy between expectations of symptom benefit and experienced benefit, women were more likely to have scores indicative of depression. This study lacked sufficient power to explore whether trait hope might mitigate the impact of such a discrepancy. These results suggest that it might be helpful to assess women's

expectations for benefit from chemotherapy in this setting. Clinicians need to balance hope giving with a realistic appraisal of likely outcomes.

Strategies for identifying and addressing unrealistic expectations in patients with advanced cancer have been proposed. The inclusion of one negative or pessimistic statement in discussions about the future may limit overly optimistic expectations³¹, while use of decision aids describing average treatment outcomes³², or various scenarios (best, worst or typical cases) for prognosis³³ have been demonstrated to be acceptable to patients³⁴. The provision of honest information did not dampen hope in one study³², suggesting honest and realistic information sensitively presented may be most effective at increasing understanding of realistic prognosis and potential benefits from treatment while maintaining hope.

The maintenance of hope is considered by many to be an important goal of palliative chemotherapy for recurrent cancer^{35,36}. Hopefulness may be protective of overall psychological well being even in the face of a terminal diagnosis: we found that trait hope was moderately correlated with psychological well being and inversely correlated with anxiety and depression before starting palliative chemotherapy.

Improvement in symptoms and overall quality of life is an important goal of treatment in recurrent ovarian cancer, and a large proportion of women in our study reported that they hoped to benefit substantially from chemotherapy ($N=91$, 73%). The dilemma for many clinicians is how to provide a balance between realistic and truthful information regarding the likelihood of symptom benefit from palliative chemotherapy while, at the same time, maintaining appropriate levels of hope²¹.

The concern that false or unrealistic hope may ultimately prove to be

disadvantageous for the patient is not unwarranted. Expectations that are unrealistically positive, for example maintaining a belief of cure in the terminal stages of an illness, can result in a lack of preparation for death that can lead to increased distress for patients and carers and exposure to avoidable futile interventions³⁷⁻⁴⁰.

In our study, patients with the greatest disparity between the improvement in symptoms they expected versus achieved, were most likely to have scores indicative of depression. While acknowledging that hope for and expectation of benefit are closely related although not identical evaluations, this suggests that encouraging unrealistic hopes for symptom benefit may be harmful.

It is unclear whether trait hope modifies the risk of developing depression when unrealistic expectations of symptom benefit are dashed. The current study was underpowered to answer this question. If this were so, it might indicate a potential protector against the disappointment of unrealised expectations, but one that is less amenable to intervention.

The nature of hope for, or expectation of, treatment benefit may change with different goals along the course of the treatment trajectory.⁴¹ It may therefore be appropriate to encourage patients to direct hope and expectation towards attainable goals that are meaningful for the individual patient⁴²⁻⁴⁴. Appropriate levels of hope are hard to define and characterise, although misguided hope is often easier to recognise⁴⁵.

The challenge for clinicians remains how to help individuals frame a difficult situation in an appropriately hopeful and helpful light. This study suggests that a smaller disparity between expectations of benefit from chemotherapy may be associated with a lower risk of developing scores indicative of clinical levels of depression.

Clinicians may be able to help lessen the disparity by encouraging hope for realistic

and achievable goals.

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