described in this Series offers a valuable guide to decision makers about how they can act now to protect the lives of a future generation of women and children.

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Effective treatment for depression in patients with cancer

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The studies by Michael Sharpe and colleagues[1] in *The Lancet* and by Jane Walker and colleagues[2] in *The Lancet Oncology* show a rigorous approach to the implementation and assessment of a complex intervention to alleviate depression in people with cancer. This research is timely, since the risk of depression has been shown to be two-to-three-times higher in patients with cancer than in the general population,[3] and could contribute to the poorer quality of life[4] and increased risk of suicide in such individuals.[5] Neurobiological factors might play a part in the link between cancer and depression,[6] but much evidence suggests that depression in this population represents a final common pathway of distress that results from the interaction of several diverse risk and vulnerability factors.[7]

Substantial advances in the treatment of cancer have been made during the past few decades, but attention to the physical and psychological symptoms of this disease and its treatment has been given lower priority in clinical settings. To address this imbalance, professional bodies have mandated that routine distress screening be a standard of practice in cancer treatment settings.[8] Such screening needs to be linked to an effective intervention programme for it to be clinically effective, although only sparse evidence has shown the benefit of such interventions in patients with cancer.[9] In other medical populations, positive outcomes in the treatment of depression have been shown to be achievable by a collaborative care approach that links care managers or nurses with primary care physicians and psychiatrists to provide and adjust psychological or pharmacological treatment, to monitor outcomes, and to ensure treatment compliance.[10]

Sharpe and colleagues have developed a collaborative care intervention for depression, which is referred to as depression care for people with cancer. This is a complex intervention involving both antidepressant medication and psychological treatment that makes available for each patient contact with, or input from, a nursing case manager trained in problem-solving therapy and behavioural activation, a primary care physician, a psychiatrist, and liaison with the patient's oncologist. The SMaRT Oncology-2 multicentre phase 3 trial of depression care for people with cancer is a major study in which 500 patients from three cancer centres in Scotland, UK, all with an expected survival of at least 12 months and a diagnosis of major depression, were randomly assigned to depression care for people with cancer or to usual care. 90% of the study population were women, and a participation rate of 47% was achieved among eligible patients. The primary outcome was treatment response at 24 weeks, defined by a 50% or greater reduction in depression severity on a self-reported measure (the Symptom Checklist Depression Scale [SCL-20]), although patients were followed for up to 48 weeks. Several other secondary and tertiary outcomes were also assessed, including depression, anxiety, physical distress, functional capacity, and quality of life.

The treatment effect in SMaRT Oncology-2 is impressive, with 62% (143 of 231) of the depression care for people with cancer group having a response at 24 weeks, compared with only 17% (40 of 231) of those in the usual care group (adjusted odds ratio 8·5 [95% CI 5·5–13·4]). Statistically significant differences were

also recorded between the two groups on all the secondary and tertiary outcomes. These benefits, which persisted throughout the trial, are greater than those reported by this group in their 2008 efficacy trial of this intervention.[11] In the present study, patients in the depression care treatment group received up to ten sessions with a nurse and were more likely to receive an effective dose of antidepressant medication than were those in the usual care group. Very few patients in the usual care group received counselling or a formal psychological intervention. The depression care intervention in this study was estimated to cost an additional £613 per patient, based on the cost of the treatment sessions, telephone contacts, and treatment supervision, although implementation in other cancer settings would incur further setup costs. How such a system of care could be implemented or modified to be feasible in lower resource settings that do not have ready access to primary care physicians, nurses, psychiatrists, and oncologists is a challenge that is yet to be addressed.

The depression care for people with cancer research group has simultaneously published a randomised controlled efficacy trial comparing this intervention to usual care for patients with lung cancer with an expected survival of at least 3 months. In this SMaRT Oncology-3 trial,[2] Walker and colleagues recruited 142 participants (43% of those eligible), all of whom had major depression. The primary outcome for this trial was depression severity (measured on the SCL-20) averaged over the time in the trial, which was chosen in part because of the potential for missing data caused by the anticipated physical decline and death of these patients. In fact, 30% (43 of 142) of the participants died during the course of the trial.

Those in the depression care for people with lung cancer group received a median of eight treatment sessions with the nurse, were more likely than were those in the usual care group to receive an effective dose of an antidepressant medication, and half of them had contact with a psychiatrist. No patient in either the treatment or control group received formal psychological treatment from non-depression care for people with lung cancer providers. Although not as dramatic as the results of SMaRT Oncology-2, a statistically significant improvement in depression severity was recorded in the depression care for people with lung cancer group (mean score on the SCL-20 1·24 [SD 0·64]) compared with the usual care group (mean score 1·61 [SD 0·58]; difference –0·38 (95% CI –0·58 to –0·18). Improvements in some of the secondary outcomes were also recorded in the depression care for people with lung cancer group compared with the usual care group.

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These two well-designed studies show that a multicomponent intervention can achieve a sustained improvement in the symptoms of depression in patients with cancer. This finding is a testament to the rigour of the studies and the nature of the treatment framework in which they took place. The individual components of the intervention are not themselves novel, but the benefit of their delivery in an integrated system of this type has not previously been shown in patients with cancer. The treatment received by the control group in both studies shows that these interventions are not routinely and consistently applied in the usual care of patients with cancer, even when they are available.

What cannot be established from the SMaRT Oncology studies is which components of this complex intervention are its most active ingredients.[12] It is not possible in these studies to disentangle the effects of the antidepressant medication, the non-specific support and close follow-up, the problem-solving and behavioural activation delivered by the nurses, or their supervisory support. Phased research[12] is needed to establish the effect of specific components, and further studies are indicated to ascertain the benefit of minimal interventions or those tailored to address problems related to the cancer type or to the stage of disease.[13] However, these two new research studies of a collaborative care intervention for depression in cancer patients represent a significant advance in knowledge

and suggest that treatments for depression delivered within such a framework might be most likely to achieve a positive outcome.

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Melanoma: immune checkpoint blockade story gets better

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The 10-year survival for patients with metastatic melanoma is less than 10%.[1] After decades of failed attempts to improve treatment outcomes in patients with this disease,[2] the recent successes with ipilimumab and the inhibitors of BRAF and MEK (vemurafenib, dabrafenib, and trametinib) have ushered in a new era in systemic therapy.[3–7] These breakthroughs have not only provided more treatment options for patients with melanoma, but have also spurred the investigation of a new generation of drugs for cancer therapy. In *The Lancet*, Caroline Robert and colleagues[8] report the results of programmed-death-receptor-1 (PD-1) blockade with pembrolizumab (MK-3475) in patients with melanoma previously treated with an anti-cytotoxic T-lymphocyte-associated-antigen-4 (CTLA-4) antibody ipilimumab; these findings are another important advance in the rapidly evolving landscape of cancer immunotherapy.

Robert and colleagues report on a randomised open-label trial expansion cohort of the phase 1 KEYNOTE-001 trial, comparing the efficacy and safety of two doses of pembrolizumab (2 mg/kg and 10 mg/kg administered intravenously every 3 weeks) in 173 patients with metastatic melanoma who had previously been treated with at least two doses of ipilimumab and had progressed within 24 weeks after the last dose of ipilimumab. Patients with a history of severe immune-related adverse events requiring prolonged (>12 weeks) treatment with steroids were not included. 64% of the study population had M1c disease and 39% had elevated lactate dehydrogenase concentrations. Treatment with both doses of pembrolizumab in this ipilimumab-treated population was associated with an objective response rate of 26%, the trial's primary endpoint; estimated progression-free survival at 24 weeks was 45% in the 2 mg/kg group and 37% in the 10 mg/kg group, and estimated 1-year overall survival was 58% and 63%, respectively. 88% of the responders were alive and progression free at the time of analysis, with at least 6 months of follow-up. Treatment was tolerated well with drug-related grade 3 to 4 adverse events reported in only 12% of patients. Only 3% of patients discontinued treatment due to drug-related adverse