Mechanisms of treatment-related symptoms in cancer patients

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Despite significant gains in our understanding of cancer biology, this progress has not matched what we know about the biology underlying the symptoms and toxic effects that therapies produce. These adverse symptoms can cause substantial discomfort, functional loss and distress to patients; they limit treatment tolerability, and can persist indefinitely in post-treatment survivorship [1]. Effective control of treatment-related symptoms could enhance therapeutic outcomes by improving patient health status, minimising toxicities that impair function, increasing adherence to curative treatments, maintaining health-related quality of life and potentially increasing survival. A mechanistic understanding of treatment-related symptoms would be of benefit in drug development, drug evaluation and early integration of appropriate supportive care in treatment planning. This presentation will present steps in a translational pathway for understanding and controlling treatment-related symptoms.

Cytotoxic therapies (chemotherapy, radiation) are expected to produce symptoms, because normal tissue and function are disrupted as cancer cells are killed. Targeted anticancer therapies were expected to destroy cancer cells specifically and therefore to cause less general toxicity, yet different and often severe toxicities have emerged, with each novel agent having its own unique toxicity profile.

1. A translational pathway for treatment-related symptoms

The difficulties inherent in translating laboratory findings into patient benefit are widely recognised in every disease area. In 2005, the National Cancer Institute created a Translational Research Working Group to speed the application of the findings of molecular oncology to patient care [2]. In response, the working group developed a model for a translational research pathway. Although the model was developed for new curative therapy, a similar model might be used to conceptualise how to move the collective basic and clinical symptom research into the clinic. A schematic illustrating such a translational pathway for symptom research is presented in Fig. 1, using fatigue as an example [3].

Early components of the pathway include discovery research steps and decision points based on longitudinal observational studies of patients, including patient interviews and determination of specific symptoms associated with disease, stage or treatment. Correlational studies showing the co-variation of biomarkers (such as inflammation) and symptom expression, although an important step, do not provide sufficient information on the mechanistic basis of symptom production for the development of potential agents targeted at symptom control. Instead, hypotheses about mechanisms underlying symptom expression are developed through examination of longitudinal symptom data, clinical correlates, biomarkers (genes, proteins) and brain imaging data obtained from patients. These hypothesised mechanisms are then tested in animal models. Candidate agents that may affect these mechanisms are developed in the laboratory, then applied in animal models of the specific disease. Agents that give some signal of effectiveness in preventing or reducing the specific cancer without excessive toxicity then move forward into patient research.

For some symptoms, such as bone-related pain, sufficient progress has been made in animal models to provide a basic understanding of the mechanisms involved and to test agents that might have a clinical benefit. In contrast, much less is known about the development of animal models of such symptoms as treatment-related cognitive impairment, fatigue and treatment-related distress. Animal models of cognitive impairment and reduced motivation are available, but the effects on these models of having cancer and being treated for cancer have not been assessed.

Biomedical research is largely dependent on having animal models of the targets of interest. The same applies to symptom science, where exploratory and confirmatory studies in humans can be conducted in parallel in animal models of symptom translational research in a bedside-to-bench and bench-to-bedside collaboration. Fatigue research is an excel-
that modulate disease and those that modulate symptoms, to ensure that symptom control does not compromise curative benefit.

Cancer-related symptoms are affected not only by treatment but also by individual host characteristics. There is substantial variation in the degree to which symptoms will impair patients, much like there is variance in the ability of a given drug to control cancer. Being able to predict this risk would benefit personalised cancer care. Potential predictors of high behavioural toxicity can be studied using advanced molecular genetic technologies. Analysis of genetic predictors for symptom occurrence and severity during treatment will help us to understand the biological basis of symptoms, identify susceptible individuals, develop tests with prognostic power, design novel drug targets and predict therapeutic outcomes.

Finally, methods to reduce treatment-related symptoms will require early clinical investigation. Too many large-scale phase III symptom-focused clinical trials have been performed with negative results. Potential reasons for this include (a) lack of knowledge of the potential mechanisms producing the symptoms, (b) inadequate preclinical testing and (c) small early trials in patients to detect a signal. Just as with curative therapies, early use of adaptive clinical trial design could be employed to sort among agents that show promise for mitigating symptoms and to quickly cull those that do not [5].

Conflict of Interest statement

None declared.

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