Does our current knowledge and evidence correspond to the values underlying the health policy debate on costly cancer medication?

Individualised treatment of metastatic cancer

The policy value base for healthcare work in Norway is not very controversial in itself. It establishes, among other things, that the seriousness of the disease must be heavily weighted when prioritising health services, and that the measures applied must have a documented effect and be reasonably cost-effective. At a meeting on cancer and priorities in spring 2012, the Director General of Health stated that there was limited documentation on the cost-effectiveness of new, expensive cancer drugs for representative patient populations (1).

As a result of systematic improvements over the past few decades that include multimodal therapy, primarily surgery and radiation, we are able as a rule to achieve long-term control of localised cancer. An example is locally advanced rectal cancer. There is consensus in the international medical community that multidisciplinary treatment tailored to the individual patient has yielded substantial returns (2).

In cases of disseminated cancer, medical tumour-directed treatment is the most important. Molecular profiling has shown that metastatic tumours are very different from the primary tumour (which is biologically heterogeneous), and that metastases are seeded by specific subclones of the primary tumour (3). Treatment of metastatic cancer should therefore be directed at molecular mechanisms in the metastatic manifestations of the disease. This is not current clinical practice, as decisions regarding therapy are almost invariably based on characteristics of the primary tumour.

A newly established national initiative, the Norwegian Cancer Genomics Consortium, outlines a scenario for medical treatment of cancer based on the individual patient's tumour biology as defined by the genetic constitution of the tumour. The development of new drugs targeting key molecular signalling pathways, and the identification of genetic mutations for these signalling molecules using modern DNA sequencing technology, form the basis for this treatment. The consortium describes this as personalised cancer medicine, and is now planning to perform cancer genome sequencing of thousands of patients and relate this information to clinical data about the disease outcome of the individual patients (4). The consortium possesses expertise in technology and in interpreting large quantities of data. In addition to fulfilling the ambition of characterising cancer genome changes in general, this expertise should be applied to prospective therapeutic studies of biologically targeted drugs for metastatic cancer. Such studies have already started at a number of cancer centres.

In the management of cancer we are always looking for evidence. The following personal views are empirical, but based on ten years of experience of treating patients with locally advanced or metastatic colorectal cancer at two of Norway's largest cancer clinics.

There is a long clinical tradition of personalised cancer therapy. All patients must feel assured that their therapy is consistent with the extent of the disease, their age, comorbidity, and no less important, their own preferences. And those of us working in this discipline, clinically as well as scientifically, must be aware of how we use the term individualised treatment when we communicate with health policymakers, to enable them to make the correct overarching prioritisations.

Metastatic cancer is the cause of extensive morbidity. For example, the disease of patients with metastatic colorectal cancer may be disseminated to the liver, lungs, peritoneum and multiple lymph node stations and skeletal locations. Given an optimised (read individualised) combination of palliative medical treatment and radiation therapy, the «average patient» may nevertheless live for a number of years. As a cancer specialist who has met hundreds of people with this diagnosis, it has often struck me that the patients may be relatively well-functioning as long as the disease manifestations are held in check. But when the metastatic disease finally becomes resistant to therapy, it progresses rapidly, both symptomatically and clinically, and the patient dies within a short period of time. In the light of my experience, I would maintain that the most important efficacy parameter in the treatment of metastatic cancer is symptom control. But this is difficult to target objectively in the absence of robust and validated tools. Progression-free survival is often the primary end-point in therapy studies for metastatic disease. In order for new therapy to be approved for use, documented efficacy, measured in terms of objective response parameters, including overall survival, is normally required. Could symptom control be developed as a more appropriate basis for these decisions?

In order to test biologically targeted drugs for metastatic cancer, we must establish new types of study design. Therapy trials with randomised patient populations and overall survival as the hard end-point are not appropriate for acquiring evidence-based knowledge for relevant cost-effectiveness. In a traditional study design of this nature, treatment response of individual patients that show correlation between a particular biomarker and an associated biologically targeted drug will «drown» in no-effect patient outcomes where there is no such correlation. An alternative strategy is the'n-of-1' trial design (5), where an objective criterion (in this case the molecular profile of the metastatic tumour) is first determined for each study patient and this then acts as its own control of the therapeutic principle (the biologically targeted drug) that is to be tested.

Such a strategy could meet both the value base criterion and the health bureaucracy's requirement that cost-effective therapy be documented in representative patient populations (which will by no means cover all patients with metastatic disease). If knowledge generated through innovative study design and alternative end-points is accepted, cost-effective, biologically targeted treatment of metastatic cancer could take its place alongside other forms of therapy.

Anne Hansen Ree
a.h.ree@medisin.uio.no

Anne Hansen Ree (born 1964) Professor of oncology at the University of Oslo and Senior Consultant at the Department of Oncology, Akershus University Hospital. She has headed a multidisciplinary research programme on functional biomarkers and trial design for biologically targeted cancer therapy for many years, and this background has led to a number of offices in European professional societies.
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