Cancer update: advances in treatment and implications for insurance medicine

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Summary

Survival of patients with cancer is steadily improving. This has been achieved largely as a result of improvements in the use of established anti-cancer treatments rather than in diagnostic techniques. Recently, agents with greater specificity against cancer have been developed and these are beginning to have an impact on survival. They include growth factor inhibitors, anti-angiogenic drugs and immunological approaches. This paper describes the implications of these developments for insurance medicine.

Introduction

The number of patients with cancer surviving for five or more years after its primary diagnosis has increased steadily over the past four decades (table 1). For breast cancer, this has occurred largely as a result of advances in the use of systemic treatments and, to a lesser extent, from the detection of early tumours by mammographic screening which may or may not have caused clinical disease during life. The enhanced curability of Hodgkin's disease and testicular cancer is also attributable to better treatment. By contrast, the longer survival rates seen in melanoma and prostate cancer have arisen entirely from an increase in the diagnosis of early non-lethal cancers rather than from any advances in treatment. Lung cancer, unfortunately, has shown little change in mortality over this time period.

Table 1. Five-year relative survival rates for specific cancers by year of diagnosis (source: http://seer.cancer.gov)

Year of diagnosis:	1970	1980	1990	2000
Breast cancer	68 %	77 %	85 %	91 %
Hodgkin's disease	67 %	75 %	82 %	87 %
Testicular cancer	72 %	92 %	96 %	96 %
Malignant melanoma	68 %	82 %	90 %	92 %
Prostate cancer	63 %	74 %	90 %	99 %
Lung cancer	10 %	14 %	14 %	16 %

Significant progress has also been seen in the survival of children with cancer (table 2), but surviving five years does not, unfortunately, predict that a normal life expectancy will be achieved as mortality in five-year survivors remains significantly above normal for at least three decades *(Moller et al., 2001)*. Although late recurrence of the original cancer continues to be a cause of death for many years, this risk diminishes with time. However, second malignancies, often caused by the late effects of cancer treatment, become increasingly important as a cause of late mortality, an effect which persists for decades *(Mertens, AC et al., 2001)*. Nevertheless, despite this problem, insurers should expect increasing numbers of young adults with a history of childhood cancer to be applicants for life, disability and critical illness policies in the years ahead.

Table 2. Five-year survival rates for childhood cancer in the USA by year of diagnosis *(Jemal A et al., 2009)*

Year of diagnosis	Five-year relative survival
1975–77	58 %
1978–80	63 %
1981–86	67 %
1987–89	71 %
1990–95	77 %
1996–2004	80 %

Improvements in the use of established anti-cancer treatments

Although major technical developments have been made in surgery and radiotherapy, it is advances in systemic treatment that have largely been responsible for the improved prognosis of many malignancies. The underlying reason for this is that, when cancer presents as a localised tumour and is radically excised with the intention of cure, recurrence occurs in a proportion of patients because of the presence of occult metastatic disease at the time of primary diagnosis

which has been unable to be identified with currently available diagnostic tests. The aim of post-operative adjuvant systemic treatment with chemotherapy and / or endocrine therapy is to destroy these unidentified micrometastases and so attempt to prevent recurrence in patients who, according to relevant prognostic factors, are predicted to be at high risk of relapse. Over the past four decades, numerous clinical trials have confirmed the effectiveness of this approach, especially in the case of breast cancer

Adjuvant! Online (https://www.adjuvantonline.com/online) is an internet service which uses data from the Surveillance, Epidemiology and End-Results (SEER) programme of the US National Cancer Institute to calculate potential risk reductions from the use of adjuvant systemic therapy determined from the statistical meta-analyses of the Early Breast Cancer Trialists' Collaborative Group *(EBCTCG 1998a /b; Ravdin PM et al., 2001)*. For a given age, state of general health and prognostic category of breast cancer, *Adjuvant! Online* provides the following proportions of patients expected ten years after primary treatment: the percentage alive, the percentage dead from breast cancer and the percentage dead from other causes. For the proportion dying as a result of breast cancer, the model estimates the reductions in deaths likely to be achieved from the use of adjuvant chemotherapy and / or endocrine therapy. The precise potential reduction in deaths varies according to the prognostic group. Overall mortality from breast cancer has dropped by some 25–30 % as a consequence of the use of adjuvant systemic treatment.

New specific anticancer treatments

Cytotoxic chemotherapy entails the use of drugs which are not specific anticancer agents, but which can indiscriminately also damage normal healthy cells. They have therapeutic activity against cancer simply because they exploit kinetic difference between normal and cancerous cells. Normal cells, particularly those in the bone marrow, have the capability, more so than malignant cells, to recover rapidly from a dose of chemotherapy. There has, therefore, been much interest recently in the development of agents which have greater specificity against cancer. These new approaches include:

- growth factor inhibitors
- anti-angiogenic agents
- immunological approaches

Some examples of recent clinical trials of these agents follow.

Growth factor inhibitors

The first drug in this category to meet with major success was *imatinib* which blocks the *bcr-abl* mutation found in chronic myeloid leukaemia (CML) thereby inhibiting the tyrosine kinase growth factor encoded by the gene. In a clinical trial with cross-over design, 1106 patients with CML were randomised to receive either imatinib or a combination of cytosine arabinoside plus interferon *(Druker BJ et al., 2006)*. At five years of follow-up, 69 % of those randomised to imatinib remained on the drug. By contrast, only 3 % of those on the combination persisted with that treatment. In the group initially randomised to imatinib, only 7 % had transformed to the blast phase and their estimated 5-year survival was 89 % (compared to 30 %–55 % for historical controls). Provided these early results persist in the long-term, the approach to underwriting applicants with CML will need to be revised.In malignant melanoma, approximately half of all cases possess a mutated gene which is inhibited by *vemurafenib*. In a clinical trial, 675 patients with metastatic disease were randomised to receive either this agent or standard chemotherapy with dacarbazine *(PB Chapman et al., 2011)*. The respective response rates were 48 % and 5 % with survival at six months being 84 % and 64 % (P <0.001). These early results suggest that vemurafenib may have potential for adjuvant treatment for high risk localised melanomas.

Sunitinib is an inhibitor of tyrosine kinases including vascular endothelial growth factor receptor and platelet-derived growth factor receptor. In a trial of 750 cases of previously untreated metastatic renal-cell carcinoma, patients were randomised to either sunitinib or standard treatment with interferon *(Motzer RJ et al., 2007)* The response rates were 31 % and 6 % (P<0.001) with median progression-free survival rates of 11 and 5 months (P<0.001) respectively; no significant difference in survival was evident at the time of this early analysis. By contrast with the above positive results, trials of the tyrosine kinase inhibitors *vandentanib*, *cediranib* and *sorafenib* have shown little effect in non-small cell lung cancer *(Morgensztern D & Herbst RS, 2012)*.

Anti-angiogenic agents

To enable their growth, tumours need to develop a blood supply and this is achieved under the influence of angiogenic growth factors produced by the neoplastic cells. *Bevacizumab* is a monoclonal antibody which prevents the formation of new blood vessels (angiogenesis) by blocking the action of vascular endothelial growth factor. In a clinical trial, 878 cases of non-small cell lung cancer were randomised to receive either chemotherapy alone or with bevacizumab *(Sandler A et al., 2006)*. The respective response rates were 15 % v 35 %, time to progression 4.5 v 6.2 months (P<0.001) and median survival 10.3 v 12.3 months (P=0.003). It remains to be seen whether or not this significant, but modest, result can be developed into a cost-effective treatment.

Immunological approaches

Hitherto, attempts to stimulate immune mechanisms against cancer have met with minimal success, but, recently, a positive result has been reported in metastatic melanoma. *Ipilimumab* is a monoclonal antibody which augments T-cell activation and proliferation. In a trial of 502 cases of metastatic melanoma, patients were randomised to receive standard chemotherapy with dacarbazine with or without ipilimumab *(Robert C et al., 2011)*. The survival rates at 1, 2 and 3 years respectively were: 47.3 % v 36.3 %, 28.5 % v 17.9 % and 20.8 % v 12.2 % (P<0.001). This positive result should lead to trials which test the possibility of ipilimumab improving survival after the surgical excision of poor-prognosis localised melanomas.

Impact of diagnostic techniques on outcomes

Anti-cancer treatments are only effective in a proportion of patients. They are expensive and often have severe side-effects. The development of diagnostic tests which could identify those patients who would respond to treatment and those who would not is, therefore, of considerable interest. The first major success in this field was the introduction of assays to determine whether or not breast cancer cells express receptors for oestrogenic hormones. Those that do so have a reasonable chance of responding to hormone treatments while those testing negative do not. Another recent example in breast cancer is the assay for the HER2-neu (c-erb-B2) receptors. If this is present, then the tumour may respond to the monoclonal antibody trastuzumab, par-

ticularly as a means of enhancing the response to cytotoxic chemotherapy.

Gene profiling (DNA microarrays) is a technique which uses multiple DNA probes to test for specific aspects of gene expression. A sample of cells is tested to find out which genes are or are not expressed. The aim is to identify specific treatments for individual patients by finding out which ones are most effective for a given combination of gene expression. Their current use is confined to research studies, but, as new drugs aimed at defined molecular targets such as growth factor inhibitors are introduced into clinical practice, the use of such tests will increase. While these tests do not improve the results from treatment per se, they contribute by assisting in avoiding the prescription of drugs to patients who predictably would not derive any benefit from them and so unnecessary adverse effects are prevented.

Conclusions

- Mortality from cancer has decreased from steady improvements in the use of long established treatments.
- New specific anticancer treatments are beginning to contribute to extending survival.
- Diagnostic advances:
  - have had relatively little impact on cancer mortality
  - assist in the selection of effective treatments and avoidance of ineffective ones
  - might have an adverse effect on critical illness insurance claims through the earlier detection of malignant disease.

Implications of advances in cancer treatment for insurance

- *Life cover:* with the improving survival prospects for patients with cancer, a reduction or, at least, delay in cancer death claims is to be expected.
- *Disability /income protection:* the longer survival being experienced by patients with cancer may give rise to an increased duration of disability claims from malignant disease.
- *Terminal illness policies:* newer agents, particularly the growth factor inhibitors, are beginning to lead to prolongation of life in cases of metastatic cancer, thereby creating difficulties in determining likely life expectancy in patients with advanced disease.
- *Impaired annuities:* the longer survival of patients with cancer

necessitates that caution is exercised by underwriters when applications for enhanced annuities are considered.

- *Critical illness insurance:* increasing numbers of cancer survivors should be expected to be applying for these policies.

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