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Circulating biomarkers in cancer care: What possible use?☆

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ABSTRACT

The practice of the physician has changed greatly in the last 100 years. Yet, the fundamental role remains constant: it is the physician's function to make a diagnosis, assess prognosis, choose and deliver the most effective treatment and then to assess the adequacy of that treatment (both in terms of effectiveness and safety). Whereas our predecessors were almost entirely reliant on clinical history and examination findings in conducting these assessments, the 21st century physician is aided by a plethora of blood tests, imaging investigations, electrophysiological recordings and morphological and molecular analyses of tissue samples. For many patients, the totality of these newer tests contributes relatively little to their journey, whilst, for some, key tests can dictate the direction of travel and, sometimes, the ultimate destination.

1. A case study: advanced prostate cancer

1.1. Presentation

A 63-year old patient presented with urinary hesitancy, increasingly frequent nocturnal micturition and back pain. Digital rectal examination revealed a hard, craggy prostate.

1.2. Diagnosis

On the given information alone, this patient was diagnosed with advanced prostate cancer with a strong suspicion of bony metastases as a cause for his back pain. A series of blood tests (totaling 38 different analytes), demonstrated a significantly elevated serum prostate specific antigen (PSA) and a moderately elevated serum alkaline phosphatase. A bone scan confirmed the presence of 2 spinal metastases at the site of his reported pain. Cross sectional imaging with computer tomography (CT) demonstrated enlarged pelvic and para-aortic lymph nodes in addition to confirming the presence of bone metastases. 12-cores taken randomly from his prostate under ultrasound guidance demonstrated high grade (Gleason sum=10) adenocarcinoma of the prostate.

1.3. Treatment

The initial treatment recommendation was life-long androgen deprivation therapy (ADT). He was also offered a 15-week course of chemotherapy using docetaxel within a clinical trial, a treatment which has subsequently proven to be effective and has become standard treatment in this setting.

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1.4. Assessment of treatment

During chemotherapy he reported expected side effects of mild nausea, hair loss and intermittent fatigue. ADT caused hotflushes, loss of libido, impotence and, almost certainly, contributed to his fatigue. His back pain resolved and his urinary symptoms improved significantly. Within 6 months, his PSA had fallen to sub-nanomolar concentrations. By 12 months, the PSA concentration appeared to have reached a nadir below the threshold of detectability in a conventional laboratory assay. Repeat imaging, however, revealed 3 new bone metastases on isotope scintigraphy, and CT demonstrated the appearance of new soft tissue masses in the liver. Biopsy of a liver mass confirmed this to be progressive prostate cancer. He subsequently received further treatment with hormonal and chemotherapies in addition to continuation of his ADT. In the two years since diagnosis he underwent 206 blood tests and 15 scans. The PSA concentration was measured 22 times.

2. Discussion

Had this patient presented 100 years previously, the diagnosis and prognosis would have been little different. The treatment, has, indeed, developed and, undoubtedly, this treatment has impacted on this patient's outcome to date. However, the multiplicity of tests performed, none of which would have been attempted in 1916, have failed to adequately address the needs of patients such as this, and the case highlights the unmet needs which could, one day, be addressed by circulating biomarkers.

2.1. Circulating biomarkers as diagnostics in cancer

Earlier diagnosis, enabling radical intervention, is widely considered to be the key to delivering more cancer cures. Many cancers, including those of the prostate, are advanced beyond curability by the time they become symptomatic (as in the case discussed above). Thus it is necessary to enable the diagnosis of cancers in asymptomatic individuals via screening programmes using low-cost, easily accessible tests such as circulating biomarkers. PSA has been widely used in the diagnostic process for men with symptoms of prostate cancer since the 1990 s and, in some countries, is employed as a screening test in asymptomatic individuals. However, formal trials of PSA screening have yielded disappointing results. In the PLCO trial [1,2] over 75,000 men were randomised to annual PSA screening versus no active screening; at follow-up after 13 years, there was no statistically significant difference in mortality rates between the two groups. A similar very large European consortium trial (European Randomised study of Screening for Prostate Cancer (ERSPC)) concluded that PSA screening reduced prostate cancer deaths by just 21% and that, to prevent one prostate cancer death, it was necessary to screen 781 men and detect (and, therefore, potentially unnecessarily treat) 27 other cancers [3]. Therefore, there is a clear need for a simple test with high specificity and sensitivity for curable, otherwise-lethal cancers, including prostate cancer. This need is only poorly met by PSA-based screening among men at risk of prostate cancer.

2.2. Circulating biomarkers as prognosticators

There is a wealth of literature concerning prognostic biomarkers in many diseases, including cancer. Most of these markers, even when strongly and independently prognostic are of only limited value in clinical practice. The ability to foretell the time of a patient's likely demise is often of little consolation if it does not affect one's ability to intervene in that process, or select patients for treatment. A significant exception to this futility is in the situation of over-diagnosis (the phenomenon seen in screening programmes where people are diagnosed with a cancer which would not otherwise have become apparent [or lethal] during their natural lifespan). As seen in the ERSPC trial [3], this can be a very significant problem potentially resulting in significant morbidity associated with excess radical interventions (such as prostatectomy or radiotherapy). Therefore circulating biomarkers which enable doctors to distinguish between non-threatening and lethal cancers (where this distinction exists, such as in prostate and breast cancer) could have very high clinical impact.

2.3. Circulating biomarkers as predictive markers

The Holy Grail of ‘Precision Medicine’ is the emerging paradigm for small numbers of patients with cancer, but one which must drive future therapeutic developments. For example, oncogenic rearrangements in the anaplastic lymphoma kinase (*ALK*) gene are present in approximately 5% of cases of non-small cell lung cancer and are predictive of response to crizotinib, an oral small molecule inhibitor of ALK tyrosine kinase, with progression-free survival in excess of that seen with standard chemotherapy [4,5]. Furthermore, the presence of a *BRAF* V600E mutation in malignant melanoma identifies a population of patients (40–60% of those diagnosed with melanoma) likely to derive benefit from BRAF inhibitors such as vemurafenib [6]. A predictive marker is one which defines a population (usually a sub-population of a conventionally-defined disease) which is more (or less) likely to benefit from a given intervention compared to the population as a whole. The ultimate goal of precision medicine is that all patients will be tested for multiple predictive markers so that each patient will receive the treatment from which they are most likely to benefit, thereby improving efficacy from effective treatment and reducing toxicity from ineffective treatment. Most truly predictive markers used in cancer treatment today are molecular pathology tests carried out in tumour specimens. These present several challenges, including the need to biopsy tumours (often repeatedly) as the molecular biology evolves during the course of the disease and the difficulties imposed by widely observed tumour heterogeneity [7]. Circulating predictive markers may overcome some of these challenges. For example, they are likely to be amenable to repeated testing in all patients (even those with difficult-to-biopsy tumours). By way of

example, it was recently found that, in patients with metastatic castrate-refractory prostate cancer, the presence of a constitutively active isoform of the androgen receptor (AR-V7) in circulating tumour cells was positively correlated with resistance to the new generation hormonal treatments abiraterone and enzalutamide [8]. Confirmatory studies aiming to establish a role for this circulating biomarker in routine care are on-going. Chronic lymphoid leukaemia (CML) is an example of a disease in which circulating biomarkers are utilised. The diagnosis of CML is made by demonstrating the presence of the oncogenic fusion protein BCR-ABL in peripheral blood by fluorescence in-situ hybridization (FISH). Thereafter, following initiation of treatment with a BCR-ABL tyrosine kinase inhibitor such as imatinib, BCR-ABL levels are checked in peripheral blood on a 3-monthly basis to determine an individual's response to treatment. If an inadequate response is observed, this would guide clinicians to consider alternative systemic treatment options, including those which target specific mutations associated with drug resistance [9,10].

More recently, advances have been made in the study of solid tumours through the identification and analysis of circulating tumour cells (CTCs) and cell-free circulating tumour DNA (ctDNA). CTCs enter the circulation from both primary and metastatic tumours. It has been established that CTCs are valid prognostic biomarkers in a number of cancer types, including metastatic castrate-refractory prostate cancer [11], metastatic breast cancer [12] and colorectal cancer [13]. Cell-free DNA (cfDNA) is typically present in the vasculature in low quantities in healthy individuals. In the context of malignancy, a proportion of cfDNA is derived from primary or metastatic tumours or CTCs. ctDNA has been evaluated as a prognostic biomarker in metastatic colorectal cancer and it has been shown that a reduction in ctDNA levels following commencement of chemotherapy was positively correlated with radiologic response to treatment [14], indicating the importance of ctDNA as a means of monitoring response. As this technology advances, it is likely that ctDNA will ultimately enable the identification of specific predictive mutations which might guide treatment choices.

2.4. Circulating biomarkers for assessment of treatment outcomes

Whilst some medical interventions are single-point-in-time treatments aimed at cure (such as antibiotic therapy for some infections) or prevention (eg. vaccination), the greatest burden on medical resources is placed on the management of chronic diseases or diseases with a high chance of recurrence. Management of many chronic diseases, including most cancers, involves the serial use of interventions, switching from one treatment to another as treatment resistance emerges. Early detection of benefit from or failure of treatment using simple biomarkers is a proven aid to the management of chronic disease (examples include blood pressure as a marker of risk for vascular disease, or glycosylated hemoglobin measurement as a marker of glycemic control in diabetes). Response-assessment biomarkers in the management of patients with cancer have a very mixed history of success. Although circulating tumour markers are in widespread use, their true value in terms of impact on outcome has been disappointing where formally tested. A randomized trial comparing CA125-guided decision making with clinical, biomarker-blind decision making in women at risk of recurrent ovarian cancer showed no discernible difference in clinical outcome [15]. Even PSA, which is widely used to detect recurrent prostate cancer after radical treatment, has unproven value as a marker to aid treatment switching in advanced disease [16], and, as the case example above reveals, it cannot be relied upon to detect significant changes in clinical disease burden.

3. Conclusions

As our understanding of disease biology has translated into more sophisticated and more numerous treatment options, it has become necessarily to find more precise ways of personalizing treatments for patients. In order to do this in cancer, the ability to repeatedly interrogate the individual patient's disease will be key to delivering better treatment outcomes in the future. Although information can be gained using multiple platforms, the potential power of circulating biomarkers which accurately reflect disease progression is great. Such markers could fulfill many of the unmet needs in modern cancer medicine, such as the need to accurately identify those in need of treatment, to select the most appropriate treatment for the individual patient, to monitor the impact of the treatment and to enable the modification of treatment when it fails.

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