Chapter 5

DETECTION, ISOLATION AND STUDY OF DISSEMINATED PROSTATE CANCER CELLS IN THE PERIPHERAL BLOOD AND BONE MARROW

Jesco Pfitzenmaier, Robert L. Vessella, William J. Ellis, Paul H. Lange

Department of Urology, University of Washington Medical School, Seattle, USA

Abstract

About 20% to 40% of men who undergo a radical prostatectomy for localized prostate cancer will relapse with progressive disease that frequently results in bone metastases. In addition to numerous studies of the primary tumour, there has been increased attention paid to disseminated cells shed by the tumour and detected in the peripheral blood and bone marrow. It would appear logical that the prostate cancer cells in the blood and the bone marrow that remain following a radical prostatectomy may be more informative in revealing prognostic information than those of the primary tumour which is removed at surgery. The evidence for existence of these disseminated cells in the peripheral blood and bone marrow of prostate cancer patients was first described in the early 1990s using a prostate specific antigen reverse transcriptase polymerase chain reaction (PSA RT-PCR). In general, these studies revealed the presence of disseminated PSA+ epithelial cells (presumed to be prostate cancer cells) early in the disease course and more prevalent in advanced disease than in early disease. Most showed that the bone marrow was more frequently positive than the peripheral blood. As a staging tool, these studies generally showed that PSA RT-PCR was not highly informative since even patients with low stage and early disease frequently showed evidence of disseminated PSA+ cells. Over the past few years, there has been a rapid development of technologies for isolating these disseminated cells for further study. The first step was the enrichment of circulating tumour cells, followed by attempts to isolate and characterize individual cells. The enriched cells have been analysed by a variety of methods, including flow cytometry, immunohistochemistry, and fluorescent *in situ* hybridisation. Biological characterisation of the cells have included the assessment of telomerase activity, androgen receptor status, and genomic alterations such as loss of heterozygosity and microsatellite instability. Attempts are under way to extend this analysis by utilizing gene expression micro-arrays and array Comparative Genomic Hybridisation (array-CGH). Although these efforts encompass challenges much will be learned about the character of these disseminated cells, including their process of trafficking to distant sites, their potential to seed and grow at these sites and their tendencies for cell dormancy.

K. Pantel (ed.), Micrometastasis, 87–116.

INTRODUCTION

Prostate Cancer

Epidemiology and Clinic

In 2001, approximately 198,000 men in the United States were diagnosed with prostate cancer, and nearly 32,000 died from this disease (1, 2). The incidence and possibly mortality has decreased, in part because of early detection efforts. Thus, in 1997, the incidence was 334,500 and the number of deaths caused by this disease was reported as 41,800 (3, 4). Among men in the industrialized countries prostate cancer is the most common cancer diagnosed and represents the second leading cause of death in male cancer patients. Over 90% of prostate cancer is diagnosed in patients between the ages of 45 and 89 years, with a median age of diagnosis of 72 years (5). The incidence rises dramatically with age. As breast cancer, prostate cancer is hormone dependent and people with a positive family history have a higher risk of developing this tumour at a younger age than patients with a negative family history. Incidence and mortality rates are considerably higher among African Americans compared to Caucasians, Asians, and Native Americans (2). The alternatives for treating a patient with localized prostate cancer are many: first, there is the watch and wait strategy that is most relevant for an older patient or a patient with a low Gleason score on biopsy that suggests a less aggressive tumour. The second and most common treatment is the radical prostatectomy (6–8) which can be performed retropubically or perineally. In many circumstances, the nerves controlling potency can be preserved. A third surgical option that is gaining acceptance for removal of the tumorous prostate is laparoscopy (9–12). For those patients who wish treatment but surgical intervention is not desired or is not an option, there is radiation therapy. External beam radiation therapy (13) is one of the two options. The second one is brachytherapy (13, 14) where the prostate gland is implanted with radioactive seeds.

The five-year survival rate for patients with a locally confined prostate cancer is 99% (4), whereas it is 93% for patients with regionally spread cancer (3). Unfortunately, even after therapy for apparently organ-confined disease, 20% to 40% of the patients have the chance of developing biochemical recurrence from persistent disease. While the clinical course of patients with elevated PSA levels are quite variable with some very long intervals between PSA elevation and clinical symptoms, eventually all of these patients will develop bone metastases if they live long enough. One key question is whether the metastases come from pre-existing micrometastases or from persistent disease remaining locally. Then, as in other kinds of malignancy, the five-year survival for a patient with distant metastases is poor, approximately 30% (3) and 0% after ten years. The palliative treatment of a patient with metastatic disease is mainly androgen ablative therapy, allowing the patient to lead a normal life with good results over several years. Because overall up to a third of the patients diagnosed with