

Review – Prostate Cancer

Achievements and Perspectives in Prostate Cancer Phase 3 Trials from Genitourinary Research Groups in Europe: Introducing the Prostate Cancer Consortium in Europe

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Abstract

Context: Phase 3 trials have made major contributions to advances in prostate cancer (PCa). However, funding limitations and excess bureaucracy are now making it difficult to conduct trials.

Objective: To describe the collaborative groups in Europe and their academic phase 3 PCa trials.

Evidence acquisition: Leaders of collaborative groups from Scandinavia, the European Organisation for Research and Treatment of Cancer (EORTC), France, Spain, the United Kingdom, Germany, Switzerland, The Netherlands, and Ireland were asked to provide information.

Evidence synthesis: Approximately 40 academic European phase 3 trials focussing on PCa have been completed, and about 10 are accruing patients. Cross-border trials have been successfully conducted led by EORTC (11), Scandinavian Prostate Cancer Group (9), European Association of Urology (1), Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficiency (STAMPEDE) (1), and the French Genito-Urinary Tumor Group (1). Among these studies were practise-changing trials showing the superiority of prostatectomy over watchful waiting in patients <65 yr of age, the benefits of combining androgen-deprivation therapy (ADT) with radiation therapy (RXT) in high-risk localised disease, the superiority of long-term versus short-term ADT, the benefit of RXT in men treated with ADT, and the role of adjuvant RXT. To bridge the numbers gap for phase 3 studies, the Prostate Cancer Consortium in Europe (PEACE) is a recently established initiative that aims to favour cross-border networks of

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investigators. PEACE 1 is testing the addition of abiraterone and that of RXT directed at the primary cancer in patients with de novo metastatic PCa treated with ADT. PEACE 2 is testing the addition of cabazitaxel and that of pelvic irradiation in patients with at least two criteria for high-risk localised PCa.

Conclusions: European academic phase 3 trials have contributed to establishing the current standard treatment of PCa. The PEACE consortium was recently tasked with the goal of addressing unanswered questions and specific biology-related issues more efficiently.

Patient summary: The Prostate Cancer Consortium in Europe was established to conduct comparative trials aiming at assessing new treatments for prostate cancer patients.

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1. Introduction

Prostate cancer (PCa) is the second most common cancer in men, and numbers continue to rise. In 2012, there were 417 000 new cases of PCa in Europe [1] compared with 370 700 in 2008 [2], although there is considerable variation in trends. Data from GLOBOCAN 2008, compiled from estimates from the International Agency for Research on Cancer, showed changes in incidence ranging from an annual decrease of 0.2% in Finland to annual increases of 2.3%, 5.4%, 7.7%, and 16.4% in Sweden, France, Poland, and Lithuania, respectively [2]. This heterogeneity is thought to reflect variations in health care services, notably the availability of prostate-specific antigen (PSA) testing [3]. PSA testing is also resulting in diagnosis at an earlier stage of disease, with fewer men having metastatic disease at diagnosis. Recent follow-up data from the European Randomised Study for Screening of Prostate Cancer show that 2.7% of men with PCa diagnosed following screening had M1 disease and/or a PSA >100, compared with 7% of those diagnosed with PCa who had not been offered screening [4]. PCa mortality is falling in most European countries [2]. During the last two decades, phase 3 clinical trials have played an important part in the improvements in PCa treatment, which, together with earlier diagnosis, are likely to have contributed to the general trend in declining mortality in Europe.

Among these studies were important phase 3 trials conducted in men with high-risk localised disease showing the benefits of combining androgen-deprivation therapy (ADT) with radiation therapy (RXT) [5], the superiority of long-term versus short-term ADT when combined with RXT [6], the benefit of RXT in men treated with ADT [7], and the role of adjuvant RXT after radical prostatectomy (RP) [8,9]. Together, these have led to major changes in clinical practice. Other key trials have included demonstration of the superiority of RP over watchful waiting in patients <65 yr of age with PCa [10].

Even with relatively small numbers of patients, such phase 3 trials have been powered to answer big questions, thanks to the large predicted gains of one treatment option over another. As the expected advantages of newer treatment options inevitably become smaller, much larger patient numbers (ie, 600–1500 patients) will be needed for future phase 3 trials aimed at further improving the prognosis for men at all stages of PCa. The growing interest in personalised medicine, based on genotypic information and biomarkers, may reduce the future need for large phase 3 trials. However,

that situation has not yet been reached for PCa and may not occur in the short to medium term, especially in producing the necessary overall survival (OS) and progression-free survival (PFS) data that currently drive clinical practice.

By grouping together into national organisations, European specialists in genitourinary (GU) cancers have gone some way to addressing the numbers gap in phase 3 clinical trials and are making significant contributions to research and best practice in GU cancer treatment. However, few of these national GU cancer groups focus solely on PCa, and most must use their membership and funding to address the needs of patients with other types of GU cancer. Pan-European organisations such as the European Organisation for Research and Treatment of Cancer (EORTC) are also playing an important role in advancing the care of patients with cancers, but they have an even broader remit than national GU cancer groups and organise clinical trials in all cancers. For these reasons, in 2012 we started to investigate the potential for a pan-European research group, open to all PCa specialists practising in the European Union (EU)-27 countries, and to those in non-EU countries, specifically to address the growing need for phase 3 clinical trials in PCa.

The objectives of this paper are briefly to describe the role of the GU groups currently involved in PCa research in Europe, to summarise the results of phase 3 trials carried out by these groups, and to discuss the potential of the new Prostate Cancer Consortium in Europe (PEACE) for conducting large rapid pan-European studies and addressing specific biology-related issues in the field of PCa research.

2. Evidence acquisition

In June 2012, we invited the European urology and oncology groups that we knew to be undertaking PCa research to participate in this review. We apologise to any groups of which we were unaware for not including them. Participating organisations were asked to summarise their objectives and achievements to date, and to provide information about their past and ongoing phase 3 trials related to treatment of all stages of PCa.

3. Evidence synthesis

3.1. Regional prostate cancer collaborative groups in Europe

Responses were received from 10 pan-European and national groups: the EORTC Genito-Urinary Cancers Group

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