Conflicts of Interest

None disclosed.

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Is angiogenesis still an attractive target in metastatic castration-resistant prostate cancer?

In this issue of *BJU International*, Karzai et al. [1] report the results of a phase I study of the anti-endoglin antibody TRC105 in patients with metastatic castration-resistant prostate cancer (mCRPC). This is a new anti-angiogenic compound with a unique mechanism of action.

Since the introduction of the concept of angiogenesis as a requirement for tumour growth and survival of solid cancers, a substantial body of research has emerged, establishing inhibition of angiogenic pathways as an important part of the armamentarium in several tumour types [2]. The idea of dynamic tumour angiogenic factors that are able to mediate neovascularisation has also been associated with tumour growth, progression and metastases in prostate cancer [1].

Some studies have revealed that microvessel density, a histological measurement of tumour angiogenesis assessed by immunohistochemical CD105 (endoglin), correlates with higher Gleason score and may predict disease progression, as well as poorer survival outcomes in patients with mCRPC. Accordingly, angiogenesis is considered an attractive target for therapeutic intervention in this disease and anti-angiogenic strategies have been studied in several clinical settings. Unfortunately, well established anti-angiogenic therapies have failed to improve survival outcomes in advanced prostate cancer. Bevacizumab or afilbercept, both combined with docetaxel, were evaluated in phase III clinical trials and no survival benefit was observed over docetaxel alone. Similarly, sunitinib was no better than placebo after chemotherapy treatment. Moreover, the recent COMET-1 trial failed to show survival benefit with cabozantinib, a dual vascular endothelial growth factor (VEGF) and MET inhibitor, in patients with mCRPC and, as a consequence, enrolment in other studies evaluating this agent has been discontinued. Strikingly, although no survival benefit has been reported, progression-free survival benefit has been observed in all of these trials.

Other anti-angionenic therapies have been investigated in patients with mCRPC. A phase II study combining thalidomide and bevacizumab with docetaxel plus prednisone showed that this is an active combination in this subset of patients. Unfortunately, the combination resulted in significant neurotoxicity and myelotoxicity, limiting its clinical use [3]. Lenalidomide was developed to have a more favourable toxicity profile compared with thalidomide and has shown activity as a single agent in patients with non-metastatic, biochemically-relapsed prostate cancer. Again, the large randomised phase III trial comparing docetaxel plus lenalidomide vs docetaxel plus placebo failed to show improvement in overall survival with the addition of this agent [4]. Finally, tasquinimod, another compound targeting angiogenesis, is under evaluation and the final results have not yet been reported. A phase III placebo-controlled study (NCT01234311), designed based on promising phase II data, is ongoing in men with mCRPC with bone metastases and is powered to detect an improvement in overall survival.

Overall, limited activity have been reported with the available agents and, until the results of the tasquinimod trial become

available, additional investigations with better-targeted therapies and tools for patient selection are needed to define how this class of agents can improve survival outcome in mCRPC. In this setting, CD105 (endoglin), a homodimeric cell membrane glycoprotein that was initially identified as a human leukaemia-associated antigen, and later also found on endothelial cells, might serve as a reasonable reference point to continue research in this direction. CD105 is a TGFβ co-receptor that is essential for angiogenesis and is selectively expressed on proliferating endothelial cells of tumour vessels. All these properties make CD105 an attractive target for drug development, as targeting the vasculature of the tumour may be more effective than conventional anti-angiogenic therapy, such as anti-VEGF therapy [5].

TRC105, an antibody to CD105, caused a overall reduction in angiogenic biomarkers and reduced tumour burden in a phase I study of advanced solid tumours at doses that were well tolerated. Karzai et al. [1] report the results of a phase I study of TRC105 in patients with mCRPC. This study was designed to define the maximum tolerated dose and to access the safety and tumour activity of TRC105 in a small cohort of patients with mCRPC. Of note, given that TRC105 has a unique mechanism of action, the toxicity profile was not similar with those commonly associated with VEGF inhibition and, at 20 mg/kg, the drug was well tolerated. Although evaluating a small number of patients, the tumour activity of this agent seems to be similar to that of the other anti-angiogenic therapies, and the potential benefit will most likely be seen when combined with other therapies. In addition, exploratory analyses have identified changes in plasma VEGF and CD105 staining on endothelial cells of tumour vessels after treatment with TRC105. These findings suggest that higher levels of VEGF are a possible compensatory mechanism for TRC105-induced anti-angiogenic activity, providing a rationale for TRC105 combination with other anti-VEGF therapies.

It has been hypothesised that endoglin-expressing vessels resist treatment, with antibody targeting the VEGF receptor by allowing continued growth of human tumour xenografts. Therefore, combining anti-angiogenic strategies with agents having different mechanisms of action may be an option to overcome resistance and produce anti-tumour responses [6]. Results from the combination of TRC105 with axitinib in patients with metastatic RCC may support this concept and are now under evaluation (NCT01806064).

Over the last 5 years, treatment of mCRPC has evolved rapidly. Immunotherapy agents (sipuleucel-T), androgen inhibitors (abiraterone acetate and enzalutamide), radioisotope (Radium-223) and cytotoxic chemotherapy (cabazitaxel) have been shown to improve overall survival in randomised phase III clinical trials. However, despite these recent advances, disease progression remains a major cause of morbidity and mortality and new therapies or combinations are required to improve patient care offering them a higher chance of achieving long-term survival.

Anti-angiogenic agents are active in certain settings of prostate cancer and some significant responses have been reported. However, a deeper understanding of the biology of mCRPC is required to characterise the complex angiogenic pathways and to elucidate mechanisms of resistance to this class of agents. This, together with the development of biomarkers to predict responses to anti-angiogenic therapies, might assist in guiding novel treatment combinations and optimising clinical benefit based on patient selection.

Conflicts of Interest

The authors declare no conflicts of interest to this work.

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