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European Journal of Cancer 41 (2005) 954–964

European Journal of Cancer

www.ejconline.com

Novel cytotoxic and biological agents for prostate cancer: Where will the money be in 2005?

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Received 18 August 2004; received in revised form 7 February 2005; accepted 8 February 2005
Available online 10 March 2005

Abstract

In 2004, docetaxel-based chemotherapy became the first treatment capable of extending life in androgen-independent prostate cancer. The era of therapeutic nihilism in this disease has thus been put to rest and a broad range of agents is being tested with the goal of improving on the successes of 2004. Lessons learned from other tumour types will need to be applied to prostate cancer in order to harness the bounty of available ideas. Target amplification or activating mutations and not merely the presence of a target are likely to be important to the success of targeted agents. Thus, the promise of the current crop of targeted agents is most likely to be realised when pursued in the context of well-credentialed targets and tested in highly translational clinical trials that are capable not only of assessing tumour response, but also of evaluating the status of the targeted pathway. The most promising agents in clinical development are reviewed.

Keywords: Prostate cancer; Chemotherapy; Targeted therapy; Novel agents

1. Introduction

In 2004, docetaxel became the first drug to prolong survival of patients with androgen-independent prostate cancer (AIPC) and the long-held view that AIPC is an untreatable disease was put to rest. The advance seen with docetaxel is critically important because it demonstrates that progress in this disease is possible and it establishes a clear standard of care upon which future studies will be built. A substantial number of investigational agents, belonging to a wide range of drug classes and targeting a broad range of cancer pathways are in clinical development. Thus, the future has never been brighter in treating this disease, which is the second-leading cancer killer of men in the United States of America (USA) and in 2000 was the cause of more than 200,000 deaths worldwide.

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doi:10.1016/j.ejca.2005.02.002

2. Current cytotoxic agents

The range of currently available cytotoxic agents has been summarised in detail by Bhandari, Petrylak and Hussain elsewhere in this volume. Active agents include mitoxantrone, the taxanes (paclitaxel and docetaxel, which seem to illustrate some schedule dependency) and estramustine [1–24]. The level of reported anti-cancer efficacy has depended somewhat on the case selection characteristics, the nature of 'response' (subjective or objective) and the use of surrogate markers of response.

3. New cytotoxic agents

3.1. SB-715992

Mitotic kinesins, which play essential roles in the assembly and function of the mitotic spindle, are

expressed preferentially in neoplastic cells. They represent novel targets for cancer treatment [25]. Inhibition of the mitotic kinesin spindle protein (KSP) results in formation of monopolar spindles within single cells and the induction of apoptosis in pre-clinical studies. SB-715992 is the first KSP inhibitor to enter clinical trials and has a broad spectrum of activity in pre-clinical models of cancer, including models that are refractory to chemotherapy and prostate cancer models. This agent has completed phase I evaluation and is entering phase II trials. The Southwest Oncology Group (SWOG) will be evaluating this agent in patients who have progressed on docetaxel-containing therapy.

3.2. Epothilones

The epothilones are a new class of cytotoxic agents with anti-neoplastic activity in pre-clinical models of a range of tumours insensitive or resistant to paclitaxel; their mechanism of action is microtubular stabilisation resulting in mitotic arrest [26]. EPO906 is a novel epothilone that is not a substrate for multidrug-resistance protein. A phase IIa trial of weekly EPO906 in 37 patients with previously-treated AIPC found that it was well tolerated; the most common adverse events were gastrointestinal. Twenty-two percent of patients responded by prostate-specific antigen (PSA) criteria and 4 out of 20 patients with measurable disease responded [27]. Two recent phase II studies demonstrate that the epothilone analogue BMS-247550 has activity in chemotherapy-naïve patients with metastatic AIPC. SWOG 0111 showed 41% PSA and 30% measurable disease response rates in patients with chemotherapy-naïve AIPC [28]. Another multi-institutional phase II study reported 56% PSA and 23% measurable disease response rates for BMS-247550 alone and 69% PSA and 44% measurable disease response rates for the combination of BMS-247550 with estramustine [29]. The most frequent grade 3 toxicities in both of these studies were fatigue and sensory neuropathy. These studies demonstrate activity for this agent, although its place in the treatment of AIPC is unclear in light of current docetaxel results. With the establishment of docetaxel-based chemotherapy as front-line therapy, suggestive evidence that there is some degree of non-cross-resistance with epothilones becomes increasingly relevant [30].

3.3. Satraplatin

Satraplatin is a novel oral platinum complex that has shown activity against AIPC in cisplatin-resistant human tumour lines and in phase I trials. Satraplatin plus prednisone was compared with prednisone alone in 50 chemotherapy-naïve AIPC patients. The satraplatin arm had a better progression-free survival (median 5.2 months *versus* 2.5 months, $P = 0.023$) and a higher frequency of PSA response (33.3% *versus* 8.7%; $P = 0.046$) [31]. A phase III trial of satraplatin plus prednisone versus prednisone as second-line chemotherapy is underway.

3.4. Amonafide

Amonafide is a synthetic imide anti-neoplastic agent with DNA intercalative properties that demonstrated significant activity in pre-clinical studies and some activity in phase I trials, including at least one partial response in a patient with prostate cancer [32]. The drug is extensively metabolised and detected in plasma and urine. Its toxicity has previously been correlated to the formation of an active metabolite, *N*-acetyl-amonafide. In phase I studies using various administration schedules of amonafide, myelosuppression was the dose limiting toxicity. A phase II trial of amonafide at a dose of 225 mg/m^2 i.v. daily for 5 d was conducted by SWOG. Forty-three evaluable patients with measurable AIPC were treated. The most common toxicities were haematological including leucopaenia (72%), granulocytopaenia (32.6%) and thrombocytopaenia (44.2%). There were no complete responses and 5 partial responses, giving an overall response rate of 12% [33].

Subsequent work determined that *N*-acetyltransferase enzyme polymorphisms play an important role in the metabolism of amonafide (fast acetylators are at great risk of haematological toxicity from amonafide therapy). Ratain and colleagues [34] proposed a pharmacodynamic model based on acetylator phenotype using caffeine as a probe to optimise amonafide dosing. Observations from a phase II trial of amonafide in patients with metastatic breast cancer that response rates appeared higher in patients experiencing more severe myelosuppression led to the hypothesis that optimisation of amonafide dosing might yield evidence of higher anti-tumour activity [35]. Using a modification of Ratain's pharmacodynamic model, a phase I/II trial of NAT2 phenotype-based dosing of amonafide is ongoing in patients with metastatic AIPC treated with up to one prior systemic chemotherapy regimen.

4. Nuclear receptor ligands

4.1. Peroxisome proliferators-activated receptor gamma (PPARγ) ligands

Peroxisome proliferators-activated receptor gamma (PPARγ) ligands are members of the nuclear receptor superfamily of ligand-dependent transcription factors and play a central role in lipid metabolism and adipocyte regulation. PPARs are widely expressed by prostate cancer cells. Synthetic PPARγ agonists inhibit prostate cancer growth *in vitro* [36]. The thiazolidinediones (including troglitazone, rosiglitazone and piaglitazone)