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CLINICAL SCIENCE REVIEW

Treatment Options in Androgen-Independent Prostate Cancer

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ABSTRACT

Metastatic prostate cancer is a leading cause of cancer-related death in men. Although most patients will respond to androgen ablation as initial systemic therapy, nearly all patients will develop androgen-independent prostate cancer (AI CaP) and will succumb to the disease. Advances in molecular biology have demonstrated mutations in and persistent expression of the human androgen receptor in metastatic disease. Furthermore, recent evidence indicates that an apoptotic block through p53 mutations or bcl-2 overexpression may have a potential role in the poor responses seen with standard chemotherapy. Presently, the six general treatment options available for AI CaP are best supportive care, radiation therapy, radioisotopes, second-line hormonal therapy, chemotherapy (single agent or combination), and investigational therapies such as monoclonal antibodies, cyclin-dependent kinase inhibitors, matrix metalloproteinase inhibitors, and antiangiogenesis agents, among others. None of these modalities have produced durable remissions, although some have demonstrated palliative benefit. The next generation of clinical trials should not consist of futile hormonal manipulations or repetitive chemotherapy. Therapeutic strategies aimed at circumventing molecular blocks to cell death or targeting unique cancer molecules and genes will be more likely to improve quality of life and longevity. Furthermore, the aggressive use of palliative care will ensure effective caring for patients and the healing of families in the absence of cure.

INTRODUCTION

Prostate cancer (CaP) will kill 39,000 men in the United States this year, making it the second leading cause of cancer-related deaths in men. The standard treatment for metastatic disease is androgen ablation, either through bilateral orchiectomy or the administration of luteinizing hormone-releasing hormone agonists. Most patients respond as evident by a fall in the levels of prostate-specific antigen (PSA), reduction in bone pain, and, when present, regression of soft tissue masses. Recently, the role of combined androgen blockade (CAB) has been questioned after a large, prospective, intergroup, randomized trial failed to show significant improvements in progression-free and overall survival in patients receiving the anti-androgen flutamide after orchiectomy compared with orchiectomy alone in patients with metastatic CaP (1). Although initially efficacious, CAB is known to cause toxicities such as fatigue, vasomotor instability, and muscle strength deterioration. Furthermore, the response to androgen deprivation is brief, with a median duration of response of 18 months (2). In those patients who receive CAB, a brief clinical response to anti-androgen withdrawal is well described and is reported in up to 30% of patients on chronic treatment (3,4). Presently, there is no consensus regarding the most appropriate second-line treatment after the development of such ''hormone refractory,'' or more accurately, ''androgen-independent'' (AI) CaP.

DEFINITION

There is presently no single definition for AI CaP because of the inexact means of determining what constitutes progressive disease in the face of maximal androgen deprivation. At the University of California Davis Cancer Center, progression is defined as an increase in the size of bidimensionally measurable metastatic disease in bone or soft tissues by at least 50% from baseline or a serum PSA of at least 10 ng/ml that has risen on three successive evaluations. Patients must have documented castrate levels of testosterone and must have discontinued anti-androgen therapy for at least a month, with one of two rising PSA determinations noted after anti-androgen withdrawal.

CaP is thought to recur despite androgen ablation because a clone of cells never responsive to maximum androgen ablation gains a growth advantage or a clone of cells with initial partial responsiveness adapts to the new milieu.

MOLECULAR CORRELATES

The role of the human androgen receptor (hAR) in the development of AI CaP has been clarified further in the past decade. The hAR is a nuclear steroid hormone receptor that binds to specific portions of the genome to stimulate transcription of ''androgen-inducible genes'' (5). AI tumors have been demonstrated to continually express high levels of hAR gene transcripts (6). Furthermore, hAR as detected by immunohistochemistry has been found in 100% of distant metastases of CaP (7). Our studies at UC Davis have demonstrated that hAR expression after CAB is seen preferentially in high-grade high-stage tumors (8). In addition, undetectable serum PSA from tumors that remain hAR positive may predict relapse after CAB. Many mutations in the hAR found in AI CaP have been described and are reviewed elsewhere (9). Altogether, these recent findings suggest that most AI CaP cells may potentially have in vivo hormone responsiveness or that an agonist binds to hAR, thus promoting disease progression.

Metastatic prostate cancer has also been shown to frequently express mutations in the p53 tumor suppressor gene (10) and increased expression of bcl-2 (11), two important cell cycle regulatory genes that modulate the apoptotic or programmed cell death pathway. Data support that mutations in cell cycle regulation influence both the natural history and response to treatment of AI CaP, leading to the development of investigational new cytotoxic agents or the identification of novel molecular targets.

TREATMENT OPTIONS

The primary goal of treatment of AI CaP, as in any other malignancy, is cure. In a population of often elderly men, symptom palliation and significant prolongation of survival (without cure) are important secondary goals. Priority should be given to accrual into clinical trials, because the current treatment options for AI CaP have largely produced disappointing results.

The six main options currently available are supportive care, external beam radiation therapy, radioisotopes, second-line hormonal therapy, chemotherapy, and investigational therapies, including suramin, novel agents, and ''targeted therapy'' such as radiolabeled monoclonal antibodies, among others.

One caveat in assessing response to systemic therapy is the evaluation of nonmeasurable disease. Decline in the serum PSA has been used as a surrogate marker, but

Table 1

Response Criteria Used in AI CaP Trials at UC Davis Cancer Center

Complete response (CR): Complete disappearance of all measurable disease with no new lesions and no disease-related symptoms. No evidence of nonassessable disease, including normalization of PSA and other abnormal lab values. For assessable disease using PSA as the primary end point, CR refers to normalization of the PSA for three successive evaluations (every 3 weeks).

Partial response (PR): Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of assessable disease or new lesions. For assessable disease using PSA as the primary end point, a decline of PSA by >80% without normalization for three successive evaluations.

Stable/no response (SD): Does not qualify for CR, PR, or progression. For assessable disease using PSA as the primary end point, patients who do not meet criteria for PR or progression for at least 90–120 days will be listed in a stable disease category.

Progression: 50% increase *or* an increase of 10 cm^2 (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, *or* clear worsening of any assessable disease, *or* reappearance of any lesion that had disappeared, *or* appearance of any new lesion/site, *or* failure to return for evaluation due to death, *or* deteriorating condition (unless clearly unrelated to prostate cancer). For assessable disease using PSA as the primary end point, at least two consecutive increases in PSA to >50% above baseline, if baseline is greater than five times the upper limit of normal.

Duration of PSA response should be at least 4 weeks.

lack of consistent criteria prevents direct comparison of "PSA response rates" across different clinical trials. Table 1 outlines the criteria used by the UC Davis Cancer Center in its current trials as approved by the National Cancer Institute.

Supportive Care

The biology of prostate cancer unfolds over years. If this process ends in AI CaP, a patient experiences transitions in medical goals from that of cure to palliation. Palliative care involves the same or more attention to the science and art of caring as the other stages.

The science includes symptom management, advanced directives, and knowledge of resources in the community. For most men, disposition of resources including estate planning is important, and the failure to address this issue is a source of significant anxiety.

The art of palliative care is to recognize the anxieties of a life-threatening illness. The care unit is the family, however defined by the patient, and the relationships that he holds most dear. The existential issues of the meaning of life are a rich source of family and physician satisfaction if sufficient time and reimbursement is allocated.

Effective palliative care does not exclude the systemic strategies discussed below, rather they are by definition palliative rather than curative. Importantly for many men, investigational therapy is a critical intervention that represents efforts at disease control. However, it is also a warning that end-of-life issues should be addressed in a meaningful way. The failure to do so results in referrals to hospice in the last week of life and a lost opportunity for a family to honor a man at his life's end.

Current reimbursement mechanisms exclude the provision of investigational therapy and hospice care. This is an irrational policy given the dual needs of patients. Until the enlightenment of reimbursement policy occurs, physicians who care for these families should recognize and initiate significant discussions of end-of-life issues.

External Beam Radiation and Radioisotopes

Both modalities have been demonstrated to be efficacious in controlling pain from metastatic deposits in bone. Focal radiation, used before the cortex is eroded by greater than 50%, can prevent pathologic fractures of weight-bearing bones. If the cortex is significantly eroded, orthopedic fixation should precede radiotherapy. External beam radiation has been reported to completely eliminate bone pain at the treated site in about 40% of patients (12).

There are currently three Food and Drug Administration-approved radioisotopes: phosphorus-32, samarium-153, and strontium-89. Phosphorus-32 was the first radioisotope used for palliation of pain from bony metastases. However, extensive osseous uptake (enhanced by pretreatment with testosterone and parathyroid hormone) leads to significant myelosuppression (13,14). Thus, phosphorus-32 has limited clinical usefulness. Samarium-153 has been shown to provide significant palliative pain relief in 70–80% of patients treated in early phase clinical trials, one of which tested the radioisotope across different malignancies metastatic to bone (15–17). Duration of pain control was brief, lasting an average of

4–8 weeks. Strontium-89, an isotope of calcium, is among the most widely used and extensively studied radionuclides. It is avidly taken up by osteoblasts. A recent review has estimated that as many as 80% of patients with painful bony metastases achieve some pain relief with strontium-89 therapy, with approximately 10% of patients becoming completely pain free (18). Other radionuclides are actively under investigation, including rhenium-186 (19) and tin-117m (20).

Second-Line Hormonal Therapy

After withdrawal from anti-androgen therapy, some patients may benefit modestly from second-line hormonal treatment, with a PSA response proportion of 14–75% (21). The hormonal agents that have been tested in early phase clinical trials include aminogluthetimide (22), high-dose bicalutamide (23,24), megestrol acetate (25), hydrocortisone (26), prednisone (27), and ketoconazole (28), among others. However, objective (measurable) responses are unusual (<5%), the duration of PSA response is only 3–4 months, and there is no improvement in overall survival.

Furthermore, in a recent trial there was rapid disease progression observed in 11 of 27 previously treated minimally symptomatic patients treated with second-line bicalutamide at a dose of 50 mg daily (29). This suggests the possibility of a "paradoxical stimulatory effect on tumor growth possibly associated with a mutant androgen receptor." In a trial using bicalutamide at 200 mg daily, "clinical benefit" was seen in some patients who had previously progressed on prior flutamide therapy (23).

Chemotherapy (Single Agent)

Nearly all classes of chemotherapeutic drugs as single agents have been used in both controlled and uncontrolled trials for AI CaP. Most antimetabolites, most alkylating agents (including melphalan, nitrogen mustard, cisplatin, and carboplatin), vinca alkaloids, and the nitrosoureas have shown little or no activity in this disease (30). Objective overall responses produced by these agents are generally under 10% (31). As would be expected, there is no improvement in overall survival with these drugs. However, pain reduction is often achieved despite lack of an objective response.

Among the most widely studied of these agents is estramustine, an alkylating agent that consists of nitrogen mustard attached to estradiol by a carbamate ester linkage. Estramustine disrupts microtubule assembly by binding to microtubule associated proteins, therefore hindering mitosis (32). In six prospective trials by the National Prostate Cancer Project using estramustine as a single agent, there were 14 objective responses out of 217 patients, for an overall response rate of 2.8% (33–38). More encouraging results were noted when estramustine was combined with other agents.

The alkylating agent cyclophosphamide has also been found to have modest activity in AI CaP. Small trials of daily oral cyclophosphamide have yielded overall responses rates ranging from 14 to 31% (39–41). Similar results were noted with intravenous high-dose cyclophosphamide, with an overall objective response rate of 30% (30). Ifosfamide as a single agent has produced disappointing results (42).

The anthracyclines doxorubicin and mitoxantrone have measurable activity against CaP. A stable disease rate of 68% and a partial response rate of 16% (by National Prostate Cancer Project criteria) have been reported for weekly intravenous doxorubicin (43). Mitoxantrone is said to have less cardiotoxicity than its older cousin doxorubicin and had been used in many early phase clinical trials for AI CaP. The PSA response rates (defined in most trials as a decrease in the serum PSA of greater than 50%) to mitoxantrone as a single agent have ranged from 13 to 30% (44,45). Clinical activity, defined as a reduction in bone pain (46), has led to further studies using mitoxantrone in combination with prednisone or hydrocortisone.

Despite broad-spectrum antitumor activity, paclitaxel has not been shown to have single-agent activity in AI CaP. The Eastern Cooperative Oncology Group conducted a phase II trial of paclitaxel using only bidimensionally measurable disease for its response criteria (47). Only one partial response out of 23 patients was observed, associated with a greater than 80% reduction in the serum PSA lasting 9 months.

The camptothecins are a novel class of anticancer agents that inhibit toposiomerase I. Topotecan, a semisynthetic camptothecin, had a 7.6% response rate in 13 patients with bidimensional measurable disease and a greater than 50% reduction in the serum PSA in 6 of 34 patients (48). A newer camptothecin analogue, 9-aminocamptothecin, has demonstrated promising preclinical activity against prostate cancer (49). Phase II trials of the original dimethylacetamide formulation are nearing completion. We are presently conducting a phase II trial of the colloidal dispersion formulation at the University of California Davis Cancer Center in collaboration with the City of Hope and University of Southern California Cancer Centers.

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