Education

Éducation

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The members of the Prostate Cancer Alliance of Canada, an umbrella group formed to carry out the recommendations of the 1997 National Prostate Cancer Forum, are pleased to support the intent to inform both health care professionals and lay people about the detection, diagnosis and treatment of prostate cancer through this 13-part series. The list of members of the Alliance appears at the end of this article.

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Clinical basics

Prostate cancer: 11. Alternative approaches and the future of treatment

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The case

A 72-year-old man with a family history of prostate cancer was treated for this disease by radical surgery 5 years ago. He has been well since but has seen friends experience relaspe and die after initial treatment with surgery or radiation treatment and subsequent drug therapy. He is aware that his sons are at increased risk for prostate cancer and asks his physician what treatments are likely to be available in the future.

Prostate cancer is a leading cause of cancer deaths in men. No study has demonstrated that any particular treatment prolongs overall survival beyond what would be expected if no treatment was undertaken. However, several studies have demonstrated that, if no treatment is undertaken, patients with moderate or high-grade prostate cancer and those with any grade of prostate cancer whose life expectancy is more than 10 years have a substantially shorter life span than men who do not have prostate cancer. Thus, most clinicians accept that selected patients will experience benefit as a result of curative treatment for prostate cancer. Furthermore, there is a considerable body of evidence for the effectiveness of different treatments in eliminating prostate cancer and prolonging cancer-free survival. In this article we discuss recent advances in surgical treatment of prostate cancer, 2 new methods of administering radiotherapy and recent developments in treatment for hormone-refractory prostate cancer.

Future surgical alternatives

The ideal treatment for localized prostate cancer remains to be determined. Most urologic surgeons believe that radical prostatectomy is the best choice for men with a life expectancy of at least 15 years and in whom the cancer is apparently localized within the prostate, is moderately or poorly differentiated and is of small to moderate volume. This belief is based on the fact that only prostatectomy offers the possibility of complete excision of the tumour. Pathological assessment of the resected specimen can be used to confirm whether excision is complete and to determine whether early adjunctive therapy might be appropriate. Prostatectomy allows for the immediate and continuous use of a biological marker, prostate-specific antigen (PSA), to monitor the success of treatment: PSA should be undetectable within a month after the procedure and should remain so. These observations have

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been bolstered by the high rate of biochemical failure (30% to 70%, determined by PSA level) associated with the only other accepted means of curing prostate cancer — traditional external-beam radiation therapy. Furthermore, changes in the selection of patients and the conduct of radical prostatectomy have increased its success and minimized both the complications and the costs of the procedure.[1]

In spite of these advantages, alternative surgical therapies have been developed to avoid the invasiveness and complications of radical prostatectomy, especially in difficult circumstances such as salvage after failed radiation therapy. The most commonly practised of these alternatives is cryosurgery. However, after its initial enthusiastic adoption, the use of this technique has declined markedly because of a high failure rate coupled with unacceptable side effects.[2,3]

Teaching points

- Most urologists believe that radical prostatectomy offers the best opportunity for cure in selected patients
- Minimally invasive treatments are now being developed that may offer the advantages of surgery with few of its complications.
- Interstitial microwave thermoablation, a still-experimental technique, involves implanting many small heat sources in the prostate to destroy localized cancer while preserving surrounding tissues.

Thermoablation of the prostate, by means of a variety of heat sources including laser, radio-frequency electromagnetic radiation, focused ultrasound and microwave energy, is another recent development.[4,5] The aim of this type of intervention is to ablate portions of the prostate surrounding the urethra and thus decrease urethral resistance. Various treatment protocols for thermoablation have met with different degrees of success.

Technological advances have allowed the development of one such treatment protocol, a minimally invasive surgical technique that offers many of the advantages of radical prostatectomy without the side effects. This technique, called interstitial microwave thermoablation, is performed by a team of urologists, medical imagers, physicists and computer experts and uses thermal energy to ablate the prostate through a percutaneous transperineal approach in a single outpatient session. This method has shown particular promise for patients in whom primary radiation therapy has failed. The heat source, which consists of a series of antennas 1.2 mm in diameter that radiate microwave energy of 912 MHz, is implanted in the prostate (Fig. 1). The theoretical ellipse-shaped heating pattern of each antenna is 3 × 2 cm. Pretreatment ultrasonography in conjunction with a 3-dimensional computer-assisted appraisal of volume and tissue consistency is used to determine the best placement sites for the antennas to ensure that the entire prostate is heated. Actual placement of the antennas is guided by transrectal ultrasonography and a template system.

The target temperature at the periphery of the gland (where the temperature will be lowest) is 60°C, and this temperature is maintained for 15 minutes. This temperature is believed adequate to completely destroy all viable cancer tissue. A small zone of urethral tissue is preserved by cooling the urethra. Although the prostate can easily be heated to very high temperatures, the surrounding tissues, such as the rectum and the penile neurovascular bundles, may be damaged by the heat applied to the prostate. To prevent harm to these structures, the technique of hydrodissection was developed. Fluid is infused into the virtual space between the prostate and rectum, separating these structures. The fluid acts as insulation, allowing constant measurement of the interface temperature and, if necessary, active cooling of the space (Fig. 2).

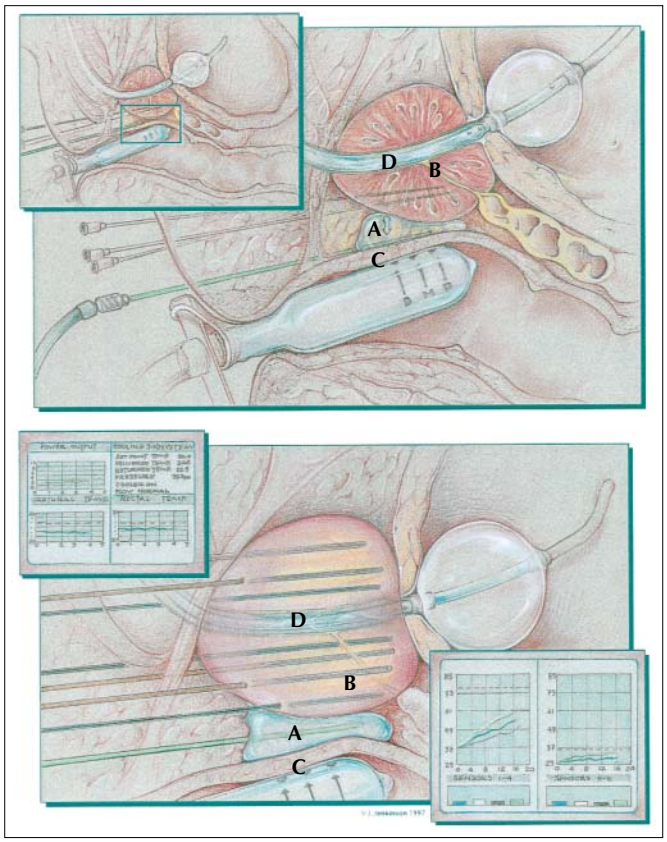

Fig. 1: Placement of microwave antennas in the prostate under ultrasound guidance for interstitial microwave thermoablation (top) and anatomic appearance during heating (bottom). The images show a hydrodissection space (A) between the prostate (B) and the rectum (C). A cooling catheter lies in the urethra (D).

Finally, online thermal imaging using phase-shift MRI has been developed to determine the actual temperature and thus to confirm that the target temperature has been reached in the prostate and that the temperature in the surrounding structures remains at a safe level.

We have used interstitial microwave thermoablation to treat a series of patients in whom primary radiation therapy for localized prostate cancer had failed (J.T., unpublished data). Recurrence of disease was documented by rising PSA levels and prostatic biopsy, and pretreatment evaluations failed to demonstrate any evidence of extraprostatic disease. We have at least 1 year of follow-up data for 13 patients whose pretreatment PSA level was less than 10 ng/mL. In 7 of these patients, the PSA level was undetectable and biopsy results were negative at 1 year (the biopsies showed only fibrous tissue with no recognizable prostatic elements). Post-treatment Doppler flow studies and gadolium-enhanced MRI in these patients suggested an absence of vascularization in what had been the prostate.

The side-effect profile of interstitial microwave thermoablation has been favourable. All patients reported perineal discomfort that could be treated with simple analgesics and that spontaneously dissipated by 1 month. There were no cases of fistulae or incontinence. The procedure can be done on an outpatient basis, although it does require general or spinal anesthesia.

Undoubtably, microwave thermoablation requires further refinement and evaluation, and it should be considered experimental. At present, it is limited to patients in whom radiation therapy has failed, in whom the residual prostate tumour is of small volume (preferably with a PSA level of less than 20 ng/mL), in whom there is no evidence of extraprostatic extension and who wish to be part of the trial at The Toronto Hospital. Nonetheless, the favourable early results are encouraging.[6,7] If future results continue to follow this trend, it might be reasonable to consider this technique as primary therapy in selected men. Interstitial microwave thermoablation offers a glimpse into the future, when total ablation of the prostate may be accomplished rapidly, safely, effectively, inexpensively and in a minimally invasive manner.

Trends in radiotherapy

Localized prostate cancer is a radiocurable disease, and recent data stratifying patients by PSA level, stage and Gleason score have levelled the playing field for comparisons of the results of surgery and radiotherapy.[8] However, 2 main factors have in the past contributed to local failure after standard radiotherapy:

- inability to deliver sufficient radiation dose to the prostate because of the radiosensitivity of the adjacent rectum and bladder
- inability to shape the radiation field to the anatomic shape of the target.

These 2 problems are clearly linked, and recent advances in imaging and in treatment planning software, in the form of 2 new delivery systems for radiotherapy, have gone a long way toward solving them. Three-dimensional conformal radiotherapy relies on external treatment beams but improves markedly the ability to shape the beams and focus treatment on the prostate while avoiding the nearby bladder and rec-

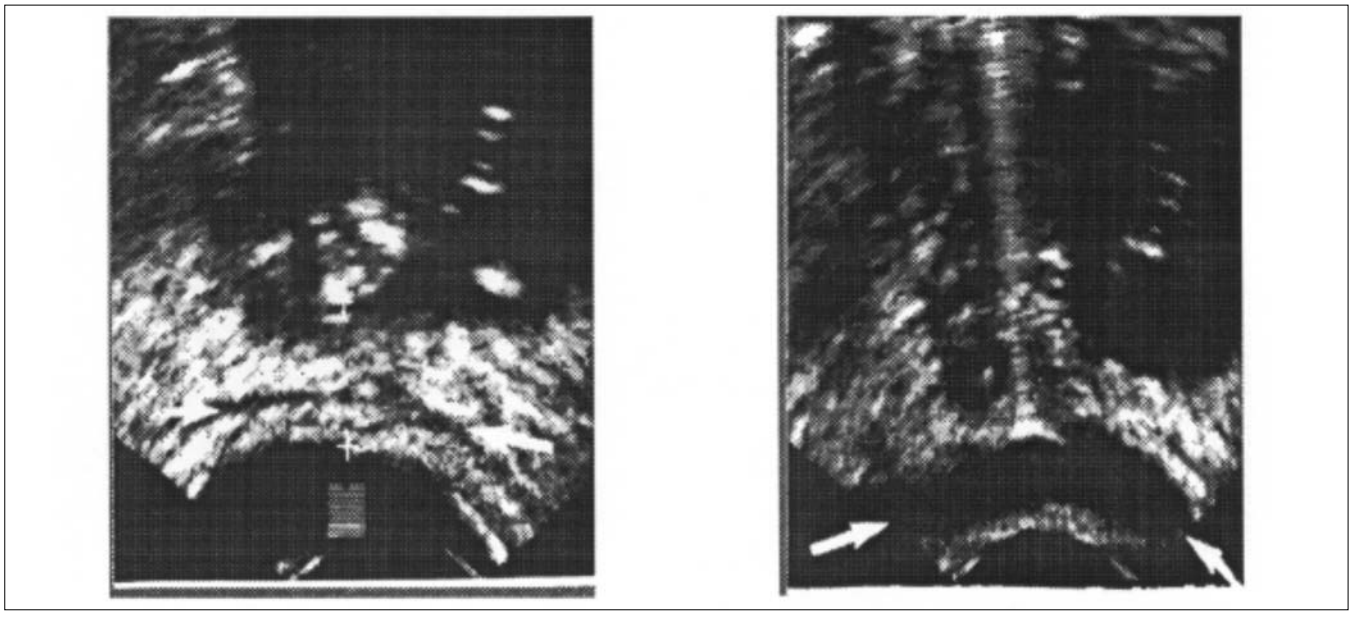

Fig. 2: Transrectal ultrasound images before (left) and after (right) infusion of fluid into the hydrodissection space. In the left-hand image, the arrows indicate a virtual space between the rectum and the prostate. In the right-hand image, the arrows point to the large space separating the rectum from the prostate, created by hydrodissection.

tum.[9] Interstitial brachytherapy involves the placement of radioactive seeds directly into the prostate to deliver the maximum dose to the prostate with a rapid decrease in dose through the rectum and bladder. Because both innovations address the problem of focusing radiation on the prostate, they permit safe delivery of a higher dose than would otherwise be possible. Although both are widely available in the United States, their use in Canada is still limited.

Conformal radiotherapy

The goal of conformal radiotherapy is to manipulate the distribution of the radiation dose so that it conforms to the shape of the target in 3 dimensions, thus minimizing the risk of missing or underdosing the target and maximizing the exclusion of normal tissue from the high-dose volume.[10]

A planning CT scan is obtained with the patient in the treatment position and immobilized in a customized cradle or shell to maximize the reproducibility of his position and to minimize daily set-up variation during the subsequent course of treatment. CT slices are obtained at 5-mm intervals through the prostate and seminal vesicles. From these images, the contours of each organ of interest (the prostate, the seminal vesicles, the rectum and the bladder) are digitized and input into the treatment planning system.

The computer program reconstructs the patient's internal anatomy in 3 dimensions and can then rotate the reconstruction in an infinite variety of ways to determine the optimal angles for beam entry and the optimal shielding of normal structures. A margin (usually 1 cm or less) must be added to the volume delineated by the CT scans to account for possible extracapsular spread, motion of the target organs within the patient and set-up variation. The treatment is then simulated according to the computer-generated plan and verified by fluoroscopy.

Customized shielding is constructed to shape each treatment beam to the anatomic target. The shielding decreases the total volume treated by as much as 40% without compromising coverage of the target and reduces the toxic effects so that doses higher than the customary 66 Gy (i.e., 76–80 Gy) can be delivered safely.

The technology exists to streamline this process so that the CT scanning and simulation are done in one suite with a single machine, a CT simulator. This instrument acquires the transverse images at 5-mm intervals, then digitally reconstructs the classic orthogonal simulator "port films," superimposing the target volume, the adjacent organs of interest and the desired shaped radiation fields.

In the past, radiation beams were defined by a standard straight collimator jaw on the machine head. To shape the beam into any form other than a rectangle or a square, customized lead-alloy shielding blocks had to be constructed for each patient and placed manually into the beam at the time of each treatment. Now, new multileaf collimators replace the standard straight collimator jaw with dozens of tiny independent segments that can be opened or closed to various degrees under computer control to achieve any field shape.

During computer-controlled radiotherapy, once the patient is positioned and immobilized on the treatment table, the linear accelerator head rotates around the patient, stopping at each predetermined beam-entry angle, shapes each beam to the desired form, administers the radiation and moves on to the next position, without the technologists having to re-enter the room, manually rotate the machine or change shielding blocks for each beam. Despite the increased complexity, the treatment can be completed in a fraction of the time of conventional external-beam radiotherapy.

Teaching points

- Radiotherapy for localized prostate cancer has been limited by physicians' inability to deliver a sufficient dose of radiation to the prostate without damaging adjacent organs.
- Advances in computer-controlled radiotherapy allow consecutive scanning of target tissue, shaping of the beam to the desired form and treatment, all within a fraction of the time usually required.
- Improved imaging sytems are increasing the effectiveness of brachytherapy: in a procedure guided by transrectal ultrasonography, needles are used to implant strings of radioactive seeds in the prostate.

Brachytherapy

Implantation of radioactive seeds in the prostate using an open but freehand suprapubic approach was popular in the late 1970s and early 1980s. The early results seemed satisfactory, with good local tumour control and minimal bladder or sexual sequelae. However, because of the inherent inhomogeneity of the freehand implantation, the long-term results were disappointing and prostate brachytherapy became unpopular for several years. Given the improved imaging made possible by transrectal ultrasonography, the problem of poor placement has been corrected, and brachytherapy is once again considered a treatment option.[10,11]

Permanent seed implants contain either iodine 125 or palladium 103. The implantation can be performed as an outpatient procedure with spinal anesthesia. Transrectal ul-

trasonography guidance is used to insert needles through the perineal skin according to a predrilled template, which ensures correct spacing. A string of radioactive seeds is inserted along each needle track. Depending on the size of the prostate, the patient will need 75 to 120 seeds.

Patients should be carefully selected for this type of treatment. They should have low-volume tumours, preferably stage T1c (found by needle biopsy after a high PSA test result) or T2a, with a Gleason score of less than 7.[10] A matched peripheral dose of 145 Gy is usually prescribed, the rectal wall receiving 100 Gy. The sequelae are acceptable and include acute proctitis (occurring in up to 25% of patients) and urethritis (dysuria, nocturia and increased frequency, which occur in up to 45% of patients and which usually last for about 2 months but can persist for up to 4–6 months). The most common late sequelae have been incontinence (in up to 5% of patients) and urethral stricture (in 12%), but the risk of these problems has been reduced recently by peripheral loading of the implants, which spares the urethra, and by avoidance of transurethral prostate resection after implantation. Prolonged urinary symptoms should be managed conservatively. Late proctitis occurs in only 3% of patients.

Teaching points

- More information about the nature of hormone-refractory prostate cancer (progression of disease after initial or sequential hormonal therapy and withdrawal of anti-androgen) is likely to come from molecular studies of the androgen receptor gene and other genes that influence its expression.
- Two treatments have been shown to relieve pain and improve the quality of life of patients with hormone-refractory prostate cancer: strontium-89 for secondary bone lesions and chemotherapy with mitoxantrone and prednisone.
- Increased understanding of the biology of prostate cancer is leading to investigation of innovative biological strategies, such as suppression of blood vessel proliferation, inhibition of growth factors, stimulation of programmed cell death, cultivation of a patient's own antigen-presenting cells and gene therapy.

Overall outlook for radiotherapy

Both 3-dimensional conformal radiotherapy and brachytherapy offer significant improvements in the ability to deliver a high dose of radiation to the prostate while sparing the radiosensitive adjacent organs. The short- and intermediate-term results for these treatments are promising. For patients with bulkier tumours or higher Gleason scores, distant failure remains a significant problem, and continuing assessment and exploration of combined modes of treatment are needed to address the systemic component of the disease.

Treating hormone-refractory prostate cancer

Hormone-refractory prostate cancer is prostate cancer that continues to progress after initial or sequential hormonal hormonal therapies to suppress the production or activity of testicular and adrenal androgens and after withdrawal of the anti-androgen.

Hormonal treatment of prostate cancer can take several forms.[12] In about 70% to 80% of patients with metastatic prostate cancer, the disease responds to primary androgen ablation therapy — orchidectomy or administration of luteininzing hormone releasing hormone (LH-RH) agonist — as indicated by relief of symptoms and a fall in the PSA level. The duration of such response is variable but averages about 1 year. Although the results of a meta-analysis[13] and a recent large US intergroup trial[14] do not suggest any survival benefit from initial combined androgen blockade, the addition of an anti-androgen at the time of disease progression can lead to a transient further response in about 30% of patients.[15] Moreover, withdrawal of the anti-androgen can also lead to a response (in terms of both symptoms and PSA level) in about 20% of patients whose disease responds to initial androgen ablation therapy.[16,17] There are also rare, but well-documented, examples of response after the reintroduction of hormonal agents in patients whose disease progressed after each of the above manoeuvres[15] and would thus have been considered hormone refractory. Although this tertiary response occurs much too rarely for reintroduction of hormone therapy to be regarded as standard management, it illustrates our limited understanding of the nature of hormonal resistance in prostate cancer.

In parallel with these observations, several recent studies have investigated genetic changes in the androgen receptor in patients with apparent hormone resistance and the influence of such changes on response to hormone manipulation in tissue culture and in animal models. Point mutations in the androgen receptor gene of prostate cancer cells generally lead to nonfunctioning of the receptor and impart resistance to further hormone manipulation.[18,19] Conversely, some tumours may develop amplification of the unmodified androgen receptor gene and may respond to further hormonal manipulation.[20]

The current definition of hormone-refractory prostate cancer will probably be modified on the basis of molecular

studies of the androgen receptor gene and other genes that influence its expression. Questions about benefit or harm from continuing or discontinuing LH-RH agonists in the face of apparent hormonal resistance will also be addressed at the clinical and molecular levels: an initial trial to address clinical aspects of this question is in progress (I.F.T., unpublished data). In the future, molecular studies of prostate cancer biopsy samples from patients whose disease appears refractory to standard endocrine therapy will be used to identify a subpopulation of patients who might benefit from further hormonal manipulation.

Treatment of symptoms

The main symptoms associated with hormone-refractory prostate cancer are pain from bone metastases and fatigue. Patients with these symptoms require optimal analgesic medication and radiation therapy for painful secondary bone lesions. This type of supportive care is likely to remain the cornerstone of patient management.

Table 1: New biological strategies for the treatment of prostate cancer

Strategy	Mechanism
Anti-angiogenesis	Tumour growth depends on new blood vessels. Tumour cells secrete growth factors (e.g., vascular endothelial growth factor) that bind to receptors on endothelial cells to stimulate their proliferation. Some agents interrupt this pathway.
Inhibition of growth-factor receptors on tumour cells	Malignant cells (including those in prostate tumours) depend on stimulating growth factors that bind to specific receptors. Some agents prevent such binding.
Differentiation therapy	Cancer cells may undergo tissue-specific differentiation or proliferation. Some agents stimulate differentiation and inhibit proliferation.
Stimulation of apoptosis	Apoptosis (programmed cell death) occurs after androgen withdrawal in hormone-sensitive prostate cancer. Stimulation of the genes that promote apoptosis (e.g., *bax*) or antisense constructs to genes that inhibit it (e.g., *bcl2*) might cause cell death in hormone-refractory prostate cancer.
Immunologic approaches	Recent advances in our understanding of the molecular complexity of the immune system allow new approaches including the isolation and cultivation of a patient's own antigen-presenting cells (dendritic cells) followed by reinfusion.
Gene therapy	Various genes can cause death of the cells into which they are introduced, either directly or by stimulating immune mechanisms. The key to this approach is to develop strategies that allow insertion of specific genes into prostate cancer cells. One method is to use viruses that seek cells producing prostate-specific antigen to insert these "suicide" genes.

There is considerable scope for improvement in pain control and in the aggressive management of the complications of narcotic medication that limit tolerance of such drugs. The routine assessment of pain during each visit to the clinic or office (for example, by the simple means of asking the patient to rate his pain on a scale of 0 to 10) can do much to improve the recognition and treatment of pain and thus to improve patients' quality of life.

Recent randomized controlled trials using validated symptomatic endpoints have shown substantial reductions in pain in patients with hormone-refractory prostate cancer who underwent one of two treatments:

- administration of strontium-89, which has physicochemical properties similar to those of calcium and is taken up by sclerotic bone ,where it provides local irradiation of bone lesions[21–23]
- chemotherapy with mitoxantrone and prednisone.[12,24]

Strontium-89, when given with conventional radiotherapy, decreased bone pain and delayed the onset of pain at new sites when given with conventional radiotherapy, relative to conventional radiotherapy alone.[21,22] Treatment with mitoxantrone (a gentle anticancer drug) and prednisone provided considerably greater and longer-duration pain relief than prednisone alone and delayed the progression of symptoms.[24] The crossover design of the trial prevented assessment of effects on survival. Mitoxantrone is well tolerated, and its use led to improvements in aspects of quality of life other than pain, as well as a greater probability of fall in PSA (a further review of the data has shown that 39% of the patients taking mitoxantrone and prednisone had a 50% or greater decrease in PSA measured on at least 2 occasions, whereas only 16% of patients taking prednisone alone showed this degree of PSA decline; $p = 0.001$). However, reduction in PSA and symptomatic response are imperfectly correlated, and the level of PSA was not at all useful in predicting the survival of patients with hormone-refractory prostate cancer.[24]

Several other anticancer drugs may lead to a decrease in PSA levels and to a decrease in pain (as assessed by physicians) in patients with hormone-refractory prostate cancer. These might provide alternatives to palliation for such patients, or they might add to the effects of mitoxantrone if used in combination with that drug. However, there is no evidence to suggest that any of the current anticancer drugs will have a major impact on survival, and the use of more toxic compounds in elderly men is likely to detract from palliation rather than add to it. Studies of high-dose mitoxantrone or highly emetogenic drugs such as cisplatin seem misguided. Mitoxantrone was chosen for study because it is a drug that is well-tolerated by older people; therefore, it would be appropriate to test other well-tolerated anticancer

drugs using similar endpoints to assess palliative benefit.

Another class of drugs, the bisphosphonates, inhibit resorption of bone and have been shown to decrease pain and improve quality of life in patients with other malignant diseases, such as breast cancer and multiple myeloma. Although secondary bone lesions from prostate cancer are largely sclerotic, preliminary evidence from phase II trials indicates that bisphosphonates might convey similar benefit to patients with hormone-refractory prostate cancer.[25] The current National Cancer Institute of Canada randomized double-blind trial for patients with symptomatic hormone-refractory prostate cancer is examining pain and quality of life in patients who receive mitoxantrone and prednisone in combination with either clodronate or placebo.

Novel approaches

Increases in our understanding of the biology of cancer, and of prostate cancer in particular, are leading to trials of strategies involving biological agents (Table 1). Because prostate cancer may progress relatively slowly (although the median survival from time of development of hormone resistance is only about 1 year), there is an opportunity to evaluate long-term treatments, such as agents to inhibit formation of the new blood vessels required for tumour growth.

Small, gradual advances are more likely to result from the approaches listed in Table 1 than dramatic breakthroughs. These agents, and others as they become available, should be evaluated in translational trials that evaluate tumour reduction or inhibition of growth, as measured by PSA and other markers; reduction of pain and other symptoms and effects on global quality of life; and genetic and cellular changes in the patient's tumour cells, to allow clinical and biological correlation.

Cancer cells are remarkably effective at becoming resistant to almost any therapy. In addition, biological therapies usually exert their greatest effects when tumours are small. Thus, if such approaches are to have an impact on the prevalence of hormone-refractory prostate cancer, they will probably have to be used in combination with hormonal manipulation at relatively early stages of disease to delay or prevent progression to the hormone-refractory state.

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