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Extracutaneous Mycosis Fungoides

ABSTRACT & COMMENTARY

Synopsis: *The prognostic factors predictive of survival outcome in patients with extracutaneous mycosis fungoides (MF) and the influence of initial skin involvement on the risk of progression to extracutaneous disease were evaluated in a study of 112 patients with extracutaneous disease at presentation or with progression and 468 patients with initial cutaneous disease only. Prognostic factors important in the cutaneous stage of disease, such as sex, race, age, extent of skin involvement, and peripheral blood Sezary cell involvement, were no longer significant to survival outcome once extracutaneous disease develops. The type and extent of skin involvement were important predictors of risk for developing extracutaneous disease in patients with initial cutaneous disease. Novel approaches to therapy are needed, as patients with extracutaneous MF have a median survival of only 13 months.*

Source: de Coninck EC, et al. *J Clin Oncol* 2001;19:779-784.

Mycosis fungoides (mf) is a cutaneous t-cell lymphoma (CTCL) of CD4+ T-cells with a usual initial presentation in the skin. This disease is rare, with an overall incidence of approximately four in 1,000,000.[1] The prognosis for patients with cutaneous disease depends on both the type and extent of cutaneous involvement. The staging for this disease takes into account the importance of different types of skin involvement, with types of skin involvement including suspicious lesions (T0), limited plaques or papules (T1), generalized plaques or papules (T2), tumors (T3), and generalized erythroderma (T4).[1] Patients with early stages of disease can have indolent, scaling patches or plaques, while patients with more advanced disease have tumors and generalized erythroderma. Additional aspects of staging include the presence of nodal involvement and the presence of visceral involvement. While several investigators have evaluated prognostic variables for patients with cutaneous MF, similar studies have not been performed for patients with extracutaneous MF.

This study by de Coninck and colleagues evaluated 112 patients with extracutaneous MF either on presentation (n = 37) to

Volume 16 • Number 3 • March 2001 • Pages 17-24

INSIDE

Bone-targeted therapy for advanced prostate cancer **page 19**

Margins in melanoma: Enough is enough **page 20**

Enoxaparin **page 21**

Dermatomyositis and polymyositis **page 22**

New screening assay for bladder cancer **page 23**

the clinic or with progression from stage I-III of disease (n = 75). In addition, another 468 patients seen in the Stanford Mycosis Fungoides Clinic within six months of their initial diagnosis were evaluated in the risk for progression analysis. The median survival from the first treatment for extracutaneous disease was 13 months (range, 8 days-more than 235 months). The survival of patients with extracutaneous MF was evaluated for prognostic groups of importance for patients with cutaneous disease, including age, sex, race, extent of skin involvement, clinical stage, and peripheral blood Sezary involvement. These prognostic factors for cutaneous MF were no longer of prognostic value for patients with extracutaneous MF. The patients received various treatments, and a complete clinical response (CR) was only obtained in 11 patients (10%). However, patients who achieved a CR had a significantly longer median survival than patients with a partial response or patients with no response (1.70 vs 0.91 years, $P = 0.047$; and 1.70 vs 0.57 years, $P = 0.011$). No correlation between specific treatment and tumor response could be made.

de Coninck et al also evaluated factors related to risk for progression in 468 patients seen within six months of their initial diagnosis. The important prognostic value of size and extent of disease were again confirmed. No patients who initially presented with T1 disease developed stage IV disease, while this outcome occurred in 2% of patients presenting with T2 disease, 13% of patients presenting with T3 disease, and 25% of patients presenting with T4 disease.

COMMENT BY MARK R. ALBERTINI, MD

Patients with extracutaneous MF have a poor prognosis, and novel treatment strategies are needed for clinical investigation for these patients. In addition, identification of prognostic factors for these patients is important for appropriate interpretation of studies evaluating systemic treatments. While several prognostic variables including age, sex, race, extent of skin involvement, clinical stage, and peripheral blood Sezary involvement are important for cutaneous MF, these factors are not of prognostic value once extracutaneous disease is present. Thus, identification of alternative prognostic markers is of importance. Several investigators have been evaluating the use of PCR to evaluate T-Cell Receptor (TCR) gene rearrangement in cutaneous MF tumors and blood.[2] The identification of a clonal T-cell population in cutaneous T-cell infiltrates has been used to help establish the diagnosis of CTCL.[2] Identical T-cell clones can also be identified in blood and in cutaneous T-cell infiltrates of MF patients.[2] However, determining whether an identical T-cell clone in blood and skin infiltrates is related to advanced disease and a poor prognosis, or corresponds to early circulation of malignant T-cells, will likely require a prospective trial.

The current markers of extent of skin involvement and peripheral blood Sezary cell involvement are of prognostic value in cutaneous MF. However, accurate prognostic factors for patients developing extracutaneous MF are needed. The prognostic value of potential prognostic markers, such as identification of identical T-cell clones in blood and cutaneous infiltrates, should be evaluated in prospective clinical studies. ❖

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Bone-Targeted Therapy for Advanced Prostate Cancer

ABSTRACT & COMMENTARY

Synopsis: *For patients with advanced, hormone refractory prostate cancer, metastatic disease in bone is a prominent cause of increased morbidity and shortened survival. Researchers from M.D. Anderson report their institution's randomized phase II trial of bone targeted consolidation therapy combining chemotherapy with strontium-89. A subset of patients (those who had responded to induction chemotherapy) was shown to have better survival if consolidation included Sr-89 plus chemotherapy when compared to chemotherapy alone. This report strengthens the rationale for bone targeted therapy in the management of prostate cancer and provides additional impetus for a large, multi-institutional phase III investigation.*

Source: Tu S-M, et al. *Lancet* 2001;357:336-341.

Prostate cancer has a predisposition to spread to bone and this leads to significant morbidity and increased mortality.[1] Specific interactions with the bone microenvironment have been implicated in this pattern and the complications that develop from progressive skeletal metastases dominate the clinical picture of advanced prostate cancer.[2] Thus, Tu and colleagues from the M.D. Anderson Cancer Center in Houston, Tex, performed a randomized trial to assess the potential role of bone-targeted therapy in patients with progressive, androgen-independent prostate cancer.

There were 105 patients included in this analysis. Two patients were enrolled but declined therapy after signing informed consent. The remaining 103 patients received induction chemotherapy consisting of doxorubicin (20 mg/m^2) as a 24-hour infusion on the first day of weeks one, three, and five and ketokonazole (400 mg) administered three times daily during those same weeks. In weeks two, four, and six, treatment consisted of vinblastine (4 mg/m^2) intravenously on the first day of the week in combination with estramustine (140 mg) orally three times daily during those same weeks. All patients also received hydrocortisone 30 mg orally in divided doses each day. Weeks seven and eight were "rest" weeks and no drugs were administered during this time. Upon completion of either two or three eight-week cycles, patients with stable or responding disease were randomized to consolidation therapy with either doxorubicin alone (at the same dose, once weekly for 6 weeks), or doxorubicin (same dose) with a single dose of strontium-89 (Sr-89); 2.035 MBq per kg body weight), given during the first week after the doxorubicin injection.

The induction chemotherapy resulted in responses (as indicated by a reduction of 50% or more in PSA concentration that persisted ≥ 8 weeks) in 62 of the 103 patients. The toxicities associated with therapy included deep vein thrombosis in 11 patients (thought to be related to indwelling venous catheters), grade 4 neutropenia in 11 patients, and grade 3 anemia in seven. Two patients died during therapy, one of a myocardial infarction and another with neutropenic sepsis.

Of the 72 patients who were considered to have either responding or stable disease after the induction chemotherapy, 36 were randomized to receive doxorubicin alone and 36 were randomized to receive doxorubicin and Sr-89. The remaining 31 patients had either progressive disease during induction therapy (n = 16), intolerable side effects (n = 9), or were lost to follow-up (n = 6). The estimated median survival for the entire group of 103 patients was 17.5 months (range, 0.5-37.7). For those that received Sr-89 and doxorubicin, the median survival was 27.7 months (4.9-37.7) and for those that received consolidation with doxorubicin alone it was 16.8 months (range, 4.4-34.2; $P = 0.0014$).

Tu et al concluded that bone-targeted consolidation therapy (with Sr-89) and continued chemotherapy offered a survival advantage for those patients with either stable or responding disease after induction chemotherapy.

COMMENT BY WILLIAM B. ERSHLER, MD

Organ directed therapy makes inherent sense for certain tumors that have a proclivity to spread predominantly to that organ. Such is the case for prostate cancer. The great majority of patients who die with prostate cancer have metastases in bone, and for most, bone is the only organ to which the disease has spread.[1] Thus, treatment that might influence tumor growth in bone is a logical therapeutic question in the management of prostate cancer. Sr-89, a bone-homing radioisotope, had already been shown to be a feasible approach and was a reasonable choice for this trial.[3]

Indeed, the patients randomized to receive Sr-89 had significantly longer time to progression and overall survival than those who did not receive Sr-89. However, as Tu et al point out, this was a relatively small, single institution study with results that might lend themselves to over interpretation. Certainly, the findings are encouraging and warrant a larger, multi-institution Phase III trial.

The mechanism of Sr-89 activity is unclear and may be related to alterations in the bone microenvironment

rather than direct prostate cancer cytotoxicity.[4] In this light, perhaps pamidronate or other bisphosphonates will also be shown to have the same effect on survival in this setting. ❖

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Margins in Melanoma: Enough is Enough

ABSTRACT & COMMENTARY

Synopsis: *The authors retrospectively studied 1155 patients with melanoma to determine the optimum excision margins. They recommend 1 cm for tumors smaller than 1 mm, 1.5 cm for tumors 1.01-2.00 mm, and 2 cm for tumors larger than 2 mm.*

Source: Ng A, et al. *Brit J Surg* 2001;88:137-142.

To determine the relationship between excision margins and local recurrence, Ng and colleagues retrospectively studied 1155 patients who were treated for melanoma at the Auckland Melanoma Unit in New Zealand. The primary melanoma lesions were separated into five groups by 1 mm increments (0-1 mm, 1-2 mm, etc.) and the excision margins were stratified by 0.5 cm intervals. Local recurrence was defined as a recurrence within 5 cm of the scar. About one-half of the local recurrences were accompanied by simultaneous regional or distant metastases.

For each thickness group, a regression analysis was performed to study the relationship between the local recurrence rate and the excision margin. The regression analysis was then used to determine the predicted minimum excision margin, termed the "optimum margin." If the surgical margins met or exceeded the optimum margin, the predicted local recurrence rate would be zero. The optimum margins were found to be 1 cm for tumors smaller than 1 mm, 1.5 cm for tumors 1.01-2.00 mm, and 2 cm for tumors larger than 2 mm.

Ng et al then applied these "optimum margins" to the entire group of patients. There was a statistically significant difference in the recurrence rate between optimally and suboptimally resected melanomas for each thickness group with the exception of lesions more than 4 mm thick. Even mortality was strongly influenced by appropriate excision margins with a *P* value of less than 0.03 for each thickness group, except tumors larger than 4 mm ($P = 0.11$). The importance of local control is suggested by the fact that 39% of patients with a local recurrence died compared with 8% without a local recurrence.

COMMENT BY KENNETH W. KOTZ, MD

With the incidence of melanoma rapidly increasing in the United States, defining the most appropriate surgical margins is of critical importance. Based on retrospective data on more than 1000 patients, Ng et al provide specific recommendations for resection margins in primary melanoma: 1, 1.5 and 2 cm for less than 1, 1.01-2 and more than 2 mm lesions, respectively.

In general, recommendations regarding the most appropriate surgical margins have been based on a number of retrospective and several prospective randomized trials. This has led to a general consensus for the following approach: 0.5 cm margins for melanoma *in situ*, 1 cm margins for melanoma less than 1 cm and 2 cm margins for melanoma 2-4 mm,[1-3] conclusions also reached by Ng et al. Unfortunately, there remains some controversy regarding those lesions over 4 mm and those with a depth of 1-2 mm.

For more than 4 mm lesions, Ng et al found the "optimum margin" to be 2 cm. Unfortunately, randomized data for these thick melanomas is lacking. Nevertheless, most authors have similar approaches, such as "at least a 2 cm margin,"[3] a "2 cm margin,"[1] and text stating, "it appears that the 2 cm margin can be safely applied" with the table stating "> 2 cm" margins.[2]

For 1-2 mm lesions, 2 cm margins are frequently advocated.[1-3] This is based in part on the World Health Organization trial which randomized 612 patients with melanomas less than 2 mm thick to 1 or 3 cm margins.[4] There were four local recurrences among the cases with 1.1-2.0 mm lesions treated with 1 cm margins vs. none for the 3 cm group. While this local recurrence rate was not statistically different, and there were no differences in disease-free or overall survival either, there remains enough of a concern that 2 cm margins continue to be widely used. Ng et al recommend margins of 1.5 cm for this group of patients. Although the study by Ng et al lacks the benefits of a prospective randomization, the wide variation in regional surgical techniques provided the advantage of being able to study a range of margins.

Because both biologic factors as well as appropriate surgical margins are likely to contribute to the risk of a local relapse,[2] there will not be any margin above which the local recurrence rate will be zero. For example, there

was still a local recurrence rate of 2.3% for lesions 1.0-2.0 mm in a trial of 742 patients randomized to either 2 or 4 cm margins.[5] Even so, care should be taken before universally adopting smaller margins because of the potentially devastating consequences of a local recurrence. On the other hand, one must also consider the long-term morbidity of the larger surgical margins, a factor not easily amenable to research, particularly in a retrospective study. Therefore, while 2 cm remains a standard for 1-2 mm melanomas, those patients requiring smaller margins for anatomical or medical considerations can be reassured that they still have an extremely low local recurrence rate. ❖

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Enoxaparin Proves Equivalent to Unfractionated Heparin for Treatment of DVT

ABSTRACT & COMMENTARY

Synopsis: *In a clinical trial of low molecular weight heparin (enoxaparin) administered either once or twice daily, comparable efficacy was demonstrated when compared to continuous, intravenous unfractionated heparin. Clinical outcomes, including the appearance of recurrent, symptomatic venous thrombosis or pulmonary emboli, were investigated. This trial provides further support for the use of LMWH in the initial management of DVT.*

Source: Merli G, et al. *Ann Intern Med* 2001;134: 191-202.

Deep vein thrombosis (dvt) remains a major cause of morbidity and mortality. Typically, patients with diagnosed DVT are treated with 5-10 days of unfractionated heparin intravenously, as initial treatment and warfarin is added within the first few days. Recently, low molecular-weight heparins (LMWH) have been introduced and have been used successfully for both prevention and treatment of DVT.[1,2] Randomized trials and meta-analysis have shown subcutaneously administered LMWH to have antithrombotic efficacy equal to (3-6) or greater than (7-9) that of continuously administered unfractionated heparin in the initial treatment of DVT, and equal to that of unfractionated heparin in the treatment of pulmonary embolism (PE).[10,11] However, many of these trials were small, did not biochemically monitor LMWH activity, and used intermediate end points, such as venographic, plethysmographic, or scintigraphic end points rather than clinical end points such as recurrent DVT or PE.

The study conducted by the Enoxaparin Clinical Trial Group (and supported by Aventis) was designed to determine whether enoxaparin administered subcutaneously once or twice per day is as effective as continuously infused unfractionated heparin in the treatment of patients with acute, symptomatic venous thromboembolic disease. Patients with acute DVT (n = 900), including 287 (32%) with pulmonary embolus, from 74 hospitals in 16 countries were randomized to receive initial therapy with dose-adjusted intravenous unfractionated heparin compared with subcutaneous enoxaparin at fixed dosages of 1.0 mg/kg of body weight twice daily or 1.5 mg/kg once daily. Long-term oral anticoagulation (warfarin) was started in all patients within 72 hours of randomization.

Equivalent efficacy was seen in the heparin group and both enoxaparin groups. Recurrent DVTs occurred in 12 of 290 patients receiving unfractionated heparin (4.1%), 13 of 298 patients receiving once daily enoxaparin (4.4%), and nine of 312 patients receiving twice daily enoxaparin (2.9%). Compared with unfractionated heparin, the treatment difference was 0.2% (95% CI, 3.04-3.49%) for once-daily enoxaparin and -1.2% (95% CI, 14.2-1.7%) for twice-daily enoxaparin. Adverse events were comparable in the three groups. Major hemorrhage occurred in six of 290 patients (2.1%) in the unfractionated heparin group, five of 298 patients (1.7%) in the once-daily enoxaparin group, and four of 312 patients (1.3%) in the twice-daily enoxaparin group.

Subgroup analysis on the basis of age, sex, weight, medical history (prior PE, presence of cancer, etc.), and location of DVT did not reveal any significant differences in either efficacy or occurrence of adverse events in any particular subgroup.

Thus, Merli and colleagues concluded that subcuta-

neous enoxaparin once or twice daily is as effective and safe as dose-adjusted, continuously infused unfractionated heparin in the prevention of recurrent symptomatic venous thromboembolic disease.

COMMENT BY WILLIAM B. ERSHLER, MD

The introduction of LMWHs to hospital and community pharmacies has been a major advance in the past decade. Physicians have been quick to use these agents because they offer the advantage of ease of treatment and reduced length of hospital stay (and, thereby, costs). Furthermore, there has been a sense that adverse events were fewer, and the incidence of treatment-associated thrombocytopenia was reduced.[12] Yet, there is also a feeling of uncertainty because laboratory monitoring is not readily available.

Thus, the current study offers reassurance for those of us who have already adopted this approach for the management of acute DVT. Furthermore, it demonstrated that once-daily injection of a larger dose of enoxaparin was equivalent to the twice-daily dose. The rationale for trying the once-daily dose was based upon pharmacokinetic studies that were specific for this particular LMWH, and should not be applied to other LMWHs, some of which already were shown to be effective at once-daily dosing. With regard to enoxaparin, however, a careful review of the data presented in this paper suggest that for the particularly high-risk patients (e.g., those with cancer, prior PE, or obesity), there was a trend, albeit, not significant, that would suggest that twice-daily dosing was more efficacious than the single dosing. Perhaps, in a larger study, these trends would reach a level of significance.

This was a carefully performed, multi-center clinical investigation with outstanding design, cautious interpretation, and a clear presentation of results. Clinical trials designed to establish comparable efficacy with an agent already known to be efficacious in a great majority of patients are complicated, require large sample sizes, and clearly stated, statistical objectives. This report is an excellent example of the way it should be done, and is recommended in that light for those developing skills in clinical trial methodology. ❖

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More on the Cancer Risks of Dermatomyositis and Polymyositis

ABSTRACT & COMMENTARY

Synopsis: *Dermatomyositis and polymyositis are uncommon disorders that have been reported to be associated with increased risk for malignancy. In this population-based study using published data from three Scandinavian countries, 198 and 137 cancers were shown to occur in 618 dermatomyositis and 914 polymyositis patients, respectively. The malignant diseases most strongly associated with dermatomyositis were ovarian, lung, gastric, colorectal and pancreatic cancers, and non-Hodgkin's lymphoma. The risk of lung and bladder cancers and non-Hodgkin's lymphoma was also increased in patients with polymyositis.*

Source: Hill CL, et al. *Lancet* 2001;357:96-100.

The association of dermatomyositis, and to a lesser extent polymyositis, has been appreciated for several decades,[1] but there have not been published series large enough to identify the specific cancer types involved. Thus, Hill and colleagues performed a pooled analysis of published national data from Sweden, Denmark, and Finland. All patients with dermatomyositis and polymyositis were identified by discharge diagnoses from the Swedish Board of Health (1964-1983), Danish Hospital Discharge Registry (1977-1989), and Finnish National Board of Health (1969-1985). These cases were matched with the national cancer registries to identify the cases of cancer that developed up to 1985 in Sweden, 1995 in Denmark, and 1997 in Finland, and to the death registries in each country for the same period. Standardized incidence ratios (SIR) for specific cancer types were calculated.

From this, 618 cases of dermatomyositis were iden-

tified, and in this cohort 198 had cancer. After the diagnosis of dermatomyositis, 115 of the 198 developed cancer. Thus, the disease was strongly associated with malignancy (SIR, 3.0, 95%; CI, 2.5-3.6), particularly ovarian (10.5, 6.1-18.1), lung (5.9, 3.7-9.2), pancreatic (3.8, 1.6-9.0), stomach (3.5, 1.7-7.3), and colorectal (2.5, 1.4-4.4) cancers and non-Hodgkin's lymphoma (3.6, 1.2-11.1).

There were 914 cases of polymyositis and 137 of these had cancer (95 after the diagnosis of polymyositis). Thus, the risk of cancer was increased in this group, but to a lesser extent than with dermatomyositis. In this group the SIR for non-Hodgkin's lymphoma was 3.7 (1.7-8.2), and lung cancer (2.8, 1.8-4.4), and bladder cancer (2.4, 1.3-4.7).

Hill et al conclude that in patients with dermatomyositis the risk of cancer of a wide range of types (particularly ovarian and lung cancer) is high. The association of cancer with polymyositis remains more modest. With either disorder, the risk of malignancy is highest at the time of myositis diagnosis.

COMMENT BY WILLIAM B. ERSHLER, MD

Dermatomyositis is an uncommon disorder and the evaluation of a large series of patients has not been possible. However, this type of analysis of registry data, which may only be possible in health care systems such as those in Scandinavia, can be very instructive. This report confirms the association of dermatomyositis (and to a lesser extent, polymyositis) with malignancy. Furthermore, the association is with a wide range of tumor types, including ovarian, lung, gastric, pancreatic, colorectal, and non-Hodgkin's lymphoma. The tumor types that develop might be different for other ethnic groups. For example, nasopharyngeal carcinoma occurs more frequently in Asian dermatomyositis patients.[2] The risk of malignancy is highest in the period around the diagnosis of myositis, but this report demonstrates a continued risk for several years thereafter. With polymyositis, the increased risk seems to disappear after a few years. Perhaps the heightened vigilance for cancer upon diagnosis of polymyositis explains the modest increase in cancer found with this diagnosis. This study also debunks the notion that dermatomyositis-associated malignancy occurs only in the elderly.[3] In this series, cancer occurred in dermatomyositis patients aged 45 and younger.

Dermatomyositis may be considered a paraneoplastic syndrome for a subset of patients. The symptoms of myositis frequently subside with effective cancer treatment, only to recur when disease relapses. There may be clinical and histological features of the myositis that are typical of cancer-associated disease. Patients with cancer-associated dermatomyositis are more likely to have normal creatinine kinase values and digital vasculitis, and less likely to have myositis associated antibodies than those without cancer.[4]

From a clinician's perspective, the importance of this study lies in the implications for malignant disease workup in patients with dermatomyositis. In view of the increased risk of ovarian, lung, gastric, colorectal, pancreatic and breast cancer, and non-Hodgkin's lymphoma, patients with dermatomyositis need a thorough evaluation and imaging studies at the time of diagnosis, and continued vigilance for the appearance of malignancy for many years thereafter. With the development of more effective therapies for these malignancies, this will become of greater importance. ❖

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A New Screening Assay for Bladder Cancer

ABSTRACT & COMMENTARY

Synopsis: *Bladder cancer is a common tumor, particularly in older individuals. Urine cytology is currently used as a screen for some high-risk individuals, but the assay lacks sensitivity. In this report, the detection of a newly described inhibitor of apoptosis (survivin) was found to be a highly sensitive indicator of active bladder cancer. Further study is needed, but it is likely that the assessment of urinary survivin will become a commonly used screening tool for the early detection and management of bladder cancer.*

Source: Smith SD, et al. *JAMA* 2001;285:324-328.

Urine cytology is currently a standard for screening high-risk individuals for bladder cancer, but its sensitivity is estimated to be only 30-40%.[1] Survivin is a recently described modulator of apoptosis[2] that has been found to be over-expressed in a wide range of tumors, including those of urinary endothelium origin.[3,4] Smith and colleagues from Yale University School of Medicine addressed the potential use of a urinary survivin assay as a

predictive/prognostic molecular marker of bladder cancer.

Five distinct groups of volunteers provided 158 urine samples for this analysis. Group 1 (n = 17) were normal, healthy controls; group 2 (n = 30) were individuals with nonneoplastic urinary tract disorders (including hematuria, infection, renal stones, etc.); group 3 (n = 30) were those with genitourinary tumors other than bladder cancer (including renal, vaginal, and prostatic); group 4 (n = 46) were those with newly diagnosed bladder cancer or those with newly discovered recurrent bladder cancer (samples taken before treatment); and group 5 (n = 35) were those receiving therapy for active disease, but with negative cystoscopic examination on the day of sampling. Urines were tested for the presence of survivin by a modified immunoassay and the results were confirmed by Western Blot and reverse transcriptase polymerase chain reaction (RT-PCR).

Survivin was detected in 100% of the urine samples from the 46 patients with new or recurrent bladder cancer but was not detected in the urine of any of the healthy volunteers or in any of those with prostate, renal, vaginal, or cervical cancer. However, of the 30 patients with non-neoplastic urinary tract disease, four patients tested positive for survivin. Of these, three had bladder abnormalities noted by cystoscopy and one had an elevated PSA level.

Smith et al conclude that the appearance of survivin in the urine was a highly sensitive and specific marker of new or recurrent bladder cancer.

COMMENT BY WILLIAM B. ERSHLER, MD

Disordered cell death (apoptosis) is currently considered a contributing factor in the development of many cancers. Survivin is one member of a gene family that inhibits apoptosis,[2] and its presence has been shown to be common in cancer cells and correlate with prognosis.[5] Accordingly, in one series, survivin was found in 78% of bladder cancers, but not in normal urothelium, and its expression correlated with accelerated recurrences.

The importance of survivin in the urine was clearly demonstrated in this report. All patients with active bladder cancer had detectable levels, whereas 32 of 35 treated patients were found to be negative. Furthermore, no survivin was detected in the urine of normal controls and when it was detected in four of 30 individuals with nonneoplastic urinary tract conditions, it was associated with an abnormal appearing bladder by cystoscopy in three and a high PSA in the fourth. Thus, the assay is both highly sensitive and specific for bladder pathology. In fact, its potential use far exceeds the current standard—urine cytology and, if these results are confirmed, it will be a significant clinical advance for bladder cancer screening.

Although the antibody used in this study to detect survivin is commercially available, standardization of the detection assay needs to be established. This, no doubt, will happen soon. Thereafter, clinician investigators will need to develop and test protocols that will ultimately determine the overall clinical use of the assay. It would seem from this work, however, that there is great potential for the measurement of urinary survivin as both a screening tool and an indicator of treatment efficacy in the management of bladder cancer. ❖

References

1. Brown FM. *Urol Clin N Amer* 2000;27:25-37.
2. Ambrosini G, et al. *Nat Med* 1997;3:917-921.
3. Velculescu VE, et al. *Nat Genet* 1999;23:387-388.
4. Dawson C, et al. *BMJ* 1996;312:1090-1094.
5. Swana HS, et al. *N Engl J Med* 1999;341:452-453.

CME Questions

13. Which of the following statements about treatment of advanced prostate with Sr-89 and doxorubicin has been demonstrated?

a. It has been shown to prolong survival in all patients.
b. It has been shown to prolong survival in all patients with bone metastases.
c. It has been shown to prolong survival as consolidation therapy for those patients who had responded (or remained clinically stable) during a course of prior induction chemotherapy.
d. All of the above
e. None of the above

14. Which of the following is true?

a. Melanomas deeper than 4 mm are best treated with 4 cm excision margins.
b. When appropriate excision margins are performed, patients can be guaranteed a local recurrence rate of 0.
c. Ng et al recommend 1.5 cm margins for melanoma lesions 1-2 mm.
d. In the study by Ng, local recurrence was not associated with survival.

15. Which of the following statements about dermatomyositis-associated malignancy is true?

a. Malignancy is most likely to antecede the diagnosis of dermatomyositis.
b. Malignancy is most frequently diagnosed within the first year after diagnosis of dermatomyositis.
c. The incidence of malignancy increases each year after the diagnosis of dermatomyositis.
d. Malignancy occurs only in elderly patients with dermatomyositis.

In Future Issues: MRI To Determine Successful Resection Margins