Patterns of Recurrence and Outcomes Following Induction Bacillus Calmette-Guerin for High Risk Ta, T1 Bladder Cancer

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Purpose: The standard approach to treatment for patients with high risk Ta, Tis, or T1 bladder cancer that persists or recurs after bacillus Calmette-Guerin is radical cystectomy in medically fit patients. Maintenance bacillus Calmette-Guerin has been shown in both SWOG (Southwest Oncology Group) and EORTC (European Organization for Research and Treatment of Cancer) studies to reduce the probability of disease worsening events. As new drugs come on line and experience with maintenance and combination immunotherapy increases, there may be a tendency to delay definitive local therapy and thereby expose patients to a higher risk of progression to invasive and potentially metastatic disease. We explored a large prospective data set from the SWOG 8507 randomized trial of maintenance bacillus Calmette-Guerin to better understand this risk and specifically to assess the impact of timing of recurrence on survival.

Materials and Methods: The database includes 501 evaluable patients who were treated with induction bacillus Calmette-Guerin and then were randomized to maintenance bacillus Calmette-Guerin or observation. Recurrence patterns were defined as early (less than 12 months following randomization) or late (12 or more months after randomization). Patients were identified who underwent cystectomy at any time after induction bacillus Calmette-Guerin. All patients were followed for life for determination of vital status. Outcome measure of overall survival was assessed using Kaplan-Meier analysis and adjustment for covariates was done with proportional hazards models. Survival was defined from date of randomization to death from any cause.

Results: A total of 501 patients were randomized after induction bacillus Calmette-Guerin, of whom 251 had recurrence and 229 died. Of the patients who died 59% had recurrence following randomization. Early recurrence was not associated with a higher risk of death compared to late recurrence ($p = 0.68$). There was no evidence that bacillus Calmette-Guerin affected the relationship of timing of relapse and survival. There was no difference in progression to T2 or greater between early and late recurrence (38 of 117, 32% vs 34 of 134, 25%; $p = 0.21$). Cystectomy was performed infrequently as 56 of 251 patients who had recurrence underwent the operation. Patients who had early recurrence had a slightly higher cystectomy rate than those with late recurrence (32 of 117, 27% vs 24 of 134, 18%; $p = 0.07$). Among 394 patients with no evidence of disease at randomization those who underwent cystectomy for T2 or greater disease had a higher risk of death compared to patients who underwent cystectomy for Tis or T1 disease (HR 1.76; 95% CI 0.77, 4.00; $p = 0.18$).

Conclusions: There was no association of the timing of recurrence after induction bacillus Calmette-Guerin on long-term survival probability. When patients had early recurrence there was a slightly higher probability of cystectomy but not progression to muscle invasive cancer. When cystectomy was performed the 5-year postoperative survival probability was lower than that reported in contemporary series.

Key Words: urinary bladder neoplasms; cystectomy; administration, intravesical; mycobacterium bovis; immunotherapy

The EORTC classifies high risk Ta, Tis and T1 bladder cancer as any high grade Ta or T1 tumor or CIS and estimates that the 5-year probability of progression is 50%. BCG is the standard treatment for these patients and complete response rates to induction therapy range from 50% to 70%. Recently the Southwest Oncology Group reported that the addition of maintenance BCG was associated with a reduction in long-term recurrence rate and improved disease-worsening survival.[1] A recent meta-analysis of 24 randomized trials demonstrated that only patients receiving maintenance BCG benefited with a reduction in risk of progression.[2]

The standard approach to treatment for patients with high risk Ta, Tis, or T1 bladder cancer that persists or recurs after BCG is radical cystectomy in medically fit patients. As new drugs come on line and experience with maintenance and combination immunotherapy increases, there may be a tendency to delay definitive local therapy and thereby expose patients to a higher risk of progression to invasive and potentially metastatic disease. For patients who do go on to cystectomy, long-term survival is significantly decreased for muscle invasive cancer compared to pT1 cancers.[3,4]

There is an inherent risk that patients who receive maintenance therapy or alternative treatment for BCG refractory

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disease may be at increased risk for progressing to muscle invasive cancer with a proportionate decrease in long-term survival. Patients with early recurrence, during or after BCG therapy, may have a biologically more aggressive cancer with a higher risk of progression compared to those with late recurrence warranting different treatment approaches. We performed an exploratory analysis of a large data set of 550 patients who were randomized in a clinical trial of maintenance BCG therapy (yes/no) following induction BCG to better understand these risks.

METHODS

The clinical trial design and analysis of outcomes for patients with no evidence of disease after induction BCG has been reported.[1] Eligible patients were BCG naïve, had completely resected Ta or T1 tumors with or without CIS and were considered to be at increased risk of recurrence. Descriptive factors (prior intravesical chemotherapy yes/no) and disease type (papillary only, carcinoma in situ only or both papillary disease and carcinoma in situ) were recorded. All patients received an induction course of BCG and randomization was to observation or maintenance BCG given weekly for three weeks at 3 and 6 months following induction and at 6-month intervals up to three years. Percutaneous BCG was administered with each intravesical dose. Those patients with disease progression during induction were not eligible to go on to randomization. A total of 660 patients were registered to undergo induction BCG, 550 were subsequently randomized and 501 were available for followup after randomization. The 501 patients included those who were not disease-free after induction BCG. Followup for disease status was discontinued after June 1996 because the clinical trial primary analysis was completed, but overall survival is current. In order for disease and survival status information to match, the survival status was truncated as of June 1996 (ie patients alive after June 1996 were censored at that time).

Outcome Measures

The term recurrence was used to define patients whose disease progressed (an increase in disease stage) or relapsed (patients who had no evidence of disease at randomization but then later had new evidence of disease). Early recurrence was defined as less than 12 months following randomization and late recurrence was defined as 12 or more months following randomization. A disease worsening event included diagnosis of T2 or greater, cystectomy, systemic chemotherapy, radiation therapy, or other therapy indicative of abandonment of strategies for treatment of superficial disease. Death from any cause was analyzed separately. Tumor stage is reported as clinical stage on the basis of bladder biopsy and/or transurethral resection.

Statistical Methods

Time to recurrence and survival estimates were determined using the Kaplan-Meier method. Survival curves were compared using the log rank test. Hazard ratios were estimated by proportional hazards regression models. Where applicable, time dependent covariates (covariates that may change in value as time progresses such as relapse and cystectomy status) were used in the models. Risk of developing muscle invasive stage or undergoing cystectomy were examined using logistic regression. Analyses presented were prepared using SPLUS® 2000 (release 3) and SAS® (version 8).

RESULTS

There were 660 patients who were registered to the trial, of whom 550 were randomized to either BCG maintenance or observation from February 1986 to April 1989. A total of 501 of the 550 patients randomized were available for followup after maintenance randomization. Of these 501 evaluable patients 251 had disease recurrence and 229 died of all causes. Among the patients who died, 59% had recurrence following randomization. Of the patients with recurrence, 117 had early recurrence and 134 had late recurrence. The proportional hazards model of survival using time dependent covariates for early recurrence and late recurrence indicates that patients who had early or late recurrence had a significantly higher risk of death relative to those patients who did not have recurrence (table 1).

The hazard ratio for death for patients who had early recurrence was 2.53 (95% CI: 1.66, 3.86; $p < 0.001$) compared with those who did not progress or relapse, whereas late recurrence was associated with a hazard ratio of 2.31 (95% CI: 1.44, 3.70; $p < 0.001$). However, early recurrence was not associated with a higher risk of death relative to late recurrence (Wald chi-square test for difference in parameter estimates for early and late recurrence $p = 0.68$). The interaction of maintenance BCG with early and late recurrence was not significant indicating that there was no evidence that BCG maintenance has a role in the relationship between timing of recurrence and survival. However, this test may be underpowered in this study. Results were similar when indicators for NED after induction BCG, age, gender, disease type (papillary/Tis) and prior intravesical chemotherapy were added to the model. The proportion of patients with disease stage T2 or greater was slightly higher among those patients with early recurrence compared to those with late recurrence (32% vs 25%, respectively) (table 2). The logistic model shows that there may be some suggestion that early recurrence leads to increased odds of muscle invasive disease with an odds ratio of 1.42 (95% CI: 0.82, 2.45; $p = 0.22$) but this was not statistically significant.

Cystectomy was performed infrequently as 56 of 251 patients with recurrence underwent the operation. Patients with early recurrence had a slightly higher cystectomy rate than did patients with late recurrence (32 of 117, 27% vs 24

TABLE 1. *Proportional hazards model of survival from maintenance randomization with early and late recurrence indicators among eligible patients*

	Hazard Ratio (95% CI)	p Value
Maintenance BCG	0.97 (0.65, 1.47)	0.90
No maintenance	1.00 (reference group)	—
Recurrence in less than 12 mos (time dependent)	2.53 (1.66, 3.86)	<0.0001
Recurrence in 12 or more mos (time dependent)	2.31 (1.44, 3.70)	0.0005
No recurrence	1.00 (reference group)	—
Interaction of BCG + late recurrence (time dependent)	1.24 (0.65, 2.35)	0.51
Interaction of BCG + early recurrence (time dependent)	1.12 (0.57, 2.19)	0.74