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# Phase II Study of Intravesical Therapy with AD32 in Patients with Papillary Urothelial Carcinoma or Carcinoma in situ (CIS) Refractory to Prior Therapy with Bacillus Calmette-Guerin (E3897): A Trial of the Eastern Cooperative Oncology Group

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## SUMMARY

**Objectives—**Assess the safety and effectiveness of AD32, a doxorubicin analogue with little systemic exposure when administered intravesically, in patients with recurrent or refractory superficial urothelial carcinoma (formerly called transitional cell carcinoma [TCC]), or carcinoma in situ (CIS), who have failed prior BCG-based immunotherapy.

**Methods—**Eligible patients received 6 weekly doses (800mg) of intravesical AD32 and were evaluated at 12-week intervals for 24 months or until date of worsening disease. Primary analysis was the proportion of all patients recurrence-free at 12 months. Treatment-related and GU-specific toxicities were also examined. All participating institutions submitted the protocol for Institutional Review Board (IRB) approval.

**Results—**The study was halted due to unavailability of study drug after accrual of 48 of a planned 64 patients; 42 were included in the analysis. Of these, 28 (67%) were still alive after median follow-up of 61.1 months. Of 21 TCC patients, 18 (85.7%) experienced disease recurrence (median time to recurrence, 5.3 months). Of the 5 CIS patients with complete response (CR), 3 (60%) experienced disease recurrence; (median time to recurrence, 37.3 months). Recurrence-free rates at 12 and 24 months were 20% (90% CI, 7.8%, 36.1%) and 15% (90 CI, 4.9%, 30.2%), respectively, for patients with TCC and 80% (90% CI, 31.4%, 95.8%) at both intervals for CIS patients with CR. Infection was the most common treatment-related toxicity; no grade 4 or higher toxicity was observed. The most common GU-specific toxicity was increased frequency/urgency.

**Conclusions—**AD32 is safe and active for treatment of recurrent or refractory superficial bladder carcinoma. The agent awaits more complete characterization when drug production problems can be solved.

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### Keywords

AD32; superficial transitional cell carcinoma; urothelial carcinoma; carcinoma in situ; bladder; intravesical

## INTRODUCTION

The optimal treatment for patients with recurrent superficial urothelial carcinoma of the bladder (stage Ta, T1 or Tis) or who fail to respond to primary intravesical treatment with bacillus Calmette-Guerin (BCG) remains controversial. Preemptive cystectomy is now advocated by many because this treatment is potentially curative if the disease is confined to the bladder. [1] However, the costs and disabilities associated with radical cystectomy and the failure to demonstrate a clear survival advantage with immediate cystectomy after failure of primary intravesical treatment, particularly when the tumor remains noninvasive,[2] continue to generate demands for new bladder-sparing approaches.

The present study is a phase 2 multi-institutional trial designed to test high-dose-intensity intravesical therapy with N-trifluoroacetyladriamycin-14-valerate (AD32, valrubicin), an anthracycline drug that has shown preliminary evidence of activity against superficial urothelial carcinoma in clinical studies sponsored by Anthra Pharmaceuticals, Inc.[3–5] In phase 1 dose-finding studies, intravesical AD32 produced very little contact toxicity and negligible systemic exposure even when administered at high dose levels (800 mg/ instillation).

## METHODS

### Patient selection

Patients were required to be >18 years of age, have a documented history of recurrent superficial bladder cancer, and have failed at least 2 courses of intravesical therapy, one of which must have been BCG. Patients were also eligible for the study if they had recurrent or persistent disease within 6 months after failing one 6-week course of BCG followed by maintenance therapy, or were unable or ineligible to complete 1 course of intravesical therapy with BCG but failed 2 prior courses of intravesical therapy with an alternative agent. In addition, no more than 2 years (24 months) could have elapsed from the end of the last cycle of intravesical therapy (immunotherapy or chemotherapy) for bladder cancer.

Eligible patients had clinically and pathologically defined papillary urothelial carcinoma (TCC, stage Ta/T1) and/or carcinoma in situ (CIS, stage Tis) of the urinary bladder, with histological and pathological analysis of biopsy samples showing no evidence of invasion of the underlying muscle (stage T2) at baseline. To stratify patients with and without CIS, investigators classified them into Group A (Ta/T1, no Tis) or Group B (Tis ± Ta/T1). For patients with CIS, biopsies must have been obtained from at least 4 sites (tumor mapping).

Eligible patients with prostatic urethral carcinoma in situ had to have undergone transurethral prostatic resection prior to initiating intravesical therapy with AD32. Within 28 days prior to registration, patients with papillary disease had to undergo complete transurethral resection (TURB) to eliminate all visible tumor, and patients with CIS must have undergone biopsy with tumor mapping.

Patients were required to have an ECOG performance status of 0–1 and adequate hepatic, renal, and hematologic function. All evaluations were to be done within 28 days of study entry.

Patients treated previously for bladder cancer with oral agents were eligible, but patients treated previously for bladder cancer with AD32, any intravenously administered systemic chemotherapy, or radiation therapy were not. Patients were ineligible if they were being treated or planning to be treated for any malignancy during the study period. Patients with a prior history of malignancy, other than superficial bladder cancer, adequately treated basal cell or squamous cell skin cancer in situ, cervical cancer, or other cancer for which the patient had been disease-free for 3 years, were ineligible. Patients must have had a normal upper urinary tract evaluation within 6 months prior to study entry. Patients were required to have no known sensitivity to anthracyclines or to Cremophor EL®, the AD32 vehicle.

All patients provided written and signed informed consent prior to study registration. All participating institutions submitted the protocol for Institutional Review Board (IRB) approval

## Treatment

Eligible patients received 6 weekly intravesical instillations of 800 mg AD32. For patients with primary CIS or stage Tis, treatment was begun within 7–28 days of prestudy evaluation; for patients with TCC or stage Ta/T1, treatment began 7–28 days following TURB.

Using aseptic technique, a total of 20 mL of AD32 solution was diluted with 55 mL sterile saline. The bladder was drained by urethral catheter prior to the instillation of the AD32 solution, which was instilled by gravitational flow via that catheter. The AD32 was to be retained in the bladder for 60–120 minutes. Patients were encouraged to be mobile during the retention time.

## Toxicity reporting

All toxicities were recorded and graded according to ECOG Common Toxicity Criteria and the Supplemental Genitourinary (GU) Toxicity Criteria for local GU toxicities. Treatment could be terminated for unacceptable toxicity, an intercurrent illness judged to potentially affect assessments of clinical status to a significant degree, and/or patient request. Patients could also be removed from the study for progressive disease. Those removed from the study prior to progression were to be followed for disease status. All patients were to be followed for survival until death.

## Measurement of efficacy

**Primary evaluation—**At 12 weeks following initiation of therapy, patients in Group A underwent cystoscopy and urine cytology. Patients in Group B were assessed by cystoscopy, bladder mapping (biopsy of $\geq 4$ sites), and urine cytology at 12 weeks. If all assessments in Group A patients were negative, the patient was categorized as complete response (CR) and continued on protocol. If cystoscopy in Group A was positive, all suspicious areas were biopsied or resected as appropriate; if pathologic analysis of biopsied or resected tissue confirmed TCC, the patient was categorized as treatment failure. In Group B, the patient was categorized as CR if all evaluations were negative, and continued on protocol. If biopsy assessment was positive, the patient was categorized as a treatment failure. All Group A and Group B patients were evaluated at 3-month intervals for 24 months. In both patient groups, if urine cytology was positive and other assessments were negative, the patient continued treatment until the next protocol-specified evaluation; if urine cytology was positive at the second evaluation, the patient was categorized as a treatment failure.

**Secondary evaluations—**All patients categorized as CR at primary evaluation were evaluated at 12-week intervals for 24 months. If cystoscopy was positive in Group A patients, suspicious areas would be biopsied or resected as appropriate. Disease recurrence was defined as positive urine cytology at 2 successive protocol-specified evaluations, and/or positive

pathologic analysis of biopsied/resected tissue in Group A, or positive biopsy for CIS or papillary TCC in Group B.

**Treatment failures—**Patients categorized as treatment failures at the primary evaluation were evaluated at 24-week intervals for 24 months or until date of worsening disease. A positive cytology was one interpreted as either “diagnostic of TCC” or “highly suggestive/suspicious for TCC”; atypia and dysplasia were not classified as positive cytologies. The first date at which disease reappeared in a patient who had been disease-free was recorded as the recurrence date. For those patients not initially classified as CR, the date of first evidence of stage T2 bladder cancer, date of cystectomy to eliminate bladder cancer, or date of first administration of systemic chemotherapy or radiation therapy to treat bladder cancer was recorded as the progression date.

**Statistical analysis—**Fisher’s exact test and Wilcoxon rank sum test were used to test whether there was significant difference with regard to patient characteristics between 2 strata. Exact binomial confidence intervals were used to describe best overall response. Kaplan-Meier analysis was used to characterize overall survival, time to recurrence, recurrence-free rate, and progression-free survival. A stratified log-rank test was used to explore the association between time to recurrence and patient characteristics. All *P*-values are two-sided.

According to the definition of recurrence, TCC patients were considered disease-free at study entry. Therefore, all TCC patients were included in the analysis of time-to-recurrence, defined as time from registration to recurrence. Only the subgroup of CIS patients who had achieved a CR could be considered disease-free and evaluated for this endpoint. Recurrence was analyzed separately for these 2 strata. Furthermore, Kaplan-Meier analysis was used to characterize recurrence-free rate to include more information on censored patients. Progression-free survival was presented to better describe disease progression for all patients on this study.

## RESULTS

The study was activated on July 2, 1998, suspended on June 4, 2002, due to issues of drug supply, reopened on June 18, 2002, and terminated on November 26, 2002, due to lack of drug availability. Final accrual to the study was 48 patients. Of these, 6 patients were ineligible (Table 1). Of the 42 patients included in the main analysis, the median age was 72 years (range: 45–89 years); 36 patients (85.7%) were male. Thirty-eight patients (95%) were white and thirty-six patients (85.7%) had an ECOG performance status of 0.

### Toxicity

Thirty-eight patients received 6 weekly treatments as planned. Treatment-related toxicities are summarized in Table 2. Infection was the most common treatment-related toxicity, but no toxicity of grade 4 or higher was observed. Among GU-specific toxicities, the most frequently occurring was increased frequency/urgency.

### Response

Table 3 summarizes both the best overall response and recurrence-free rate. For TCC patients, the proportion of patients with CR as best overall response was 42.9% (90% CI: 24.5%, 62.8%). Five CRs were observed among CIS patients with a response rate of 23.8% (90% CI: [9.9%, 43.7%]). Two TCC patients were unevaluable for response.

### Overall survival and follow-up

Survival time was defined as time from registration to death (from any cause). As of the last patient census, 14 of the 42 eligible patients (33.3%) died, 6 of them from bladder cancer. Therefore, median survival had not been reached. Median follow-up among surviving patients was 61.1 months. The survival rate at 5 years was 68.3% (90% CI: 54.6%; 78.7%).

Of the 21 TCC patients (Group A), 5 (23.8%) died. Median follow-up of those still alive was 63.8 months. The 5-year survival rate for TCC was 76.2% (CI 90%: 56.6%, 87.8%).

Of the 21 CIS patients (Group B), 9 (42.9%) died. Median follow-up among surviving CIS patients was 55.6 months. The survival rate at 5 years was 59.7% (90% CI: 39.0%, 75.4%), with a median survival of 61.4 months.

### Time to recurrence versus disease-free rates

Of the 21 TCC patients, 18 (85.7%) experienced disease recurrence, and median time to recurrence was 5.3 months. Of the 5 CIS patients with CR, 3 (60%) experienced disease recurrence, and median time to recurrence was 37.3 months.

Of all the factors considered in the recurrence analysis, which included age, gender, initial or entry T stage, entry tumor grade, and multiple tumors at diagnosis or entry, only solitary versus multiple tumors at entry significantly predicted median time to recurrence. Among the 26 patients included in recurrence analysis (21 TCC and 5 CIS with CR), patients with multiple tumors at study entry had shorter time to recurrence (median, 3.0 months) than patients without multiple tumors at study entry (median, 9.4 months) after adjusting for stratum ($P$= 0.01). Recurrence-free rates for TCC patients at 12 and 24 months were 20% (90% CI: 7.8%–36.1%) and 15% (CI, 4.9%, 30.2%), respectively. For the 5 CIS patients who had achieved CR, recurrence-free rates at 12 and 24 months from the date of CR were both 80% (90% CI, 31.4%, 95.8%)(see Table 3).

### Progression-free survival

Progression-free survival was defined as time from registration to progression or death, whichever occurred first. Of the 21 TCC patients, 9 progressed or died, and median progression-free survival is 22.4 months. Twelve CIS patients progressed or died, for a median progression-free survival of 8.7 months.

## DISCUSSION

Intravesical immunotherapy with BCG remains the gold standard for primary intravesical treatment of superficial bladder cancer,[6,7] and it demonstrably reduces the rates of disease progression and death due to bladder cancer.[8] However, while most patients tolerate treatment with intravesical BCG, local toxicity is common, and systemic BCG infection has been reported.[9,10] In addition, 30% to 60% of patients either fail to respond to BCG or recur following a primary response.[6,11,12] The risk of tumor progression to muscle invasion or metastasis varies directly with tumor stage,[13,14] but a significant proportion of recurrences remain superficial TCC.[2,13]

Cystectomy in this situation can be curative, and a recent review of historical cohort data from Memorial Sloan-Kettering has suggested that the trend toward preemptive cystectomy for patients with T1 bladder carcinoma has been associated with improved outcome.[15] Preemptive cystectomy has also been recommended for CIS.[16] However, its social and financial costs are high, and there are patients who will refuse it. Efforts to find options for these patients remain valid. In addition, an earlier study from this same center, reviewing data

from 41 patients who failed primary treatment with intravesical BCG, indicated no survival advantage among those with less invasive stages of superficial bladder cancer for patients treated immediately with cystectomy vs patients treated with cystectomy following failure of a second course of intravesical therapy.[2]

Newer intravesical immunotherapy strategies have shown encouraging results in phase 1–2 studies, but the overall quality of the evidence is poor, and clarification probably awaits better appreciation of the molecular immunology of the interface between these agents—including BCG—and tumor tissues.[7,17] Likewise, the role of intravesical chemotherapy in recurrent superficial bladder cancer, particularly in treatment of recurrent lower grade tumors, remains imperfectly defined. A meta-analysis of 22 controlled studies of intravesical chemotherapy concluded that treatment did not significantly reduce the long-term tumor recurrence, progression, and patient survival rates after primary adjunctive treatment or with maintenance treatment.[6] More recent analyses are equally discouraging, while at the same time recognizing that intravesical chemotherapy continues to have some role even in recurrent disease for some individuals.[1,18–20]

In the US, thiotepa is the only chemotherapeutic agent that has FDA registration for intravesical administration, although mitomycin C and doxorubicin are also used in clinical practice.[21] The main toxicities of intravesical chemotherapy are irritative bladder symptoms. More severe, drug-specific side effects, including myelosuppression, systemic allergic reactions, contact toxicity, and bladder fibrosis leading to contracture, occur in 10%–20% of patients.

AD32 has novel pharmacologic and pharmacokinetic properties. AD32 is a highly lipophilic analogue of doxorubicin (DOX or Adriamycin®) that, unlike doxorubicin, traverses cell membranes rapidly, does not bind to or intercalate with DNA, is metabolized extensively, and is eliminated rapidly.[22–24] Systemic exposure to the drug or its metabolites is minimal if administered intravesically,[4,25] and administration immediately after TURB is feasible.[5] Earlier clinical studies of intravenously administered AD32 showed no evidence of cardiotoxicity, even in patients who received high cumulative doses,[26,27]and less gastrointestinal toxicity and alopecia than doxorubicin. AD32 also did not produce local tissue irritation when the drug was extravasated inadvertently during administration. Further, intravesical AD32 does not appear to adversely affect hematopoiesis, and GU-specific toxicity with intravesical administration appears to be mainly associated with instillation and has not been significantly different than with other intravesically administered agents. Experience with AD32 in this study supports this relatively benign picture. Unfortunately, this data is not definitive, owing to drug production problems.

The study was designed to distinguish a 35% recurrence-free rate at 12 months from a 21% rate, the historical norm. Assuming accrual of 64 eligible patients, AD32 would be considered worthy of further study if 18 or more patients had remained recurrence-free at 12 months. Given this design, the study had approximately 90% power with a one-sided alpha level of 0.109. Unfortunately, owing to problems with supply of the study drug, it was not possible to reach the accrual goal. In addition, according to the definition of recurrence, only a subgroup of CIS patients who had achieved CR could be considered disease-free and evaluated for this endpoint, which contributed to the effect of diminished total numbers. In future studies, the proportion of patients potentially available for such subanalyses should be taken into consideration.

## SUMMARY AND CONCLUSIONS

In this truncated study, recurrence of superficial bladder cancer after intravesical therapy with high-dose AD32 was roughly equal to the historical norm [4] for this patient group. Overall

safety and tolerability remain good. Our data suggest that additional exploration of AD32 should be pursued if the associated production issues can be resolved.

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**Table 1**

Reasons for exclusion of 6 patients

| Stratum | Status | Reason |
|---|---|---|
| CIS | Ineligible | Prior malignancy and invasive TCC ($T_3$) at baseline |
| CIS | Ineligible | Carcinoma in situ without required bladder mapping |
| CIS | Did not start assigned therapy | Patient decided to have cystectomy instead |
| TCC | Did not start assigned therapy | Gross hematuria developed |
| TCC | Did not start assigned therapy | Lack of drug availability |
| Unknown | Ineligible | No urothelial carcinoma at study entry |

CIS, carcinoma in situ; TCC, transitional cell carcinoma

**Table 2**

Treatment-related toxicities and supplemental GU toxicities

| | N=45 Grade | | |
|---|---|---|---|
| | 1 (n) | 2 (n) | 3 (n) |
| **General treatment-related toxicity type** | | | |
| Leukopenia | 1 | - | - |
| Granulocytopenia | 1 | - | - |
| Thrombocytopenia | 1 | - | - |
| Anemia | 5 | - | 1 |
| Hemorrhage | - | 1 | - |
| Infection | 1 | 5 | 1 |
| Fever(No Infection) | 2 | 1 | - |
| Nausea/vomiting | 3 | - | - |
| Diarrhea | 1 | - | - |
| Liver | 3 | - | - |
| Skin | 3 | - | - |
| Alopecia | 1 | - | - |
| Weight Gain | 1 | - | - |
| Weight Loss | 1 | - | - |
| Abdominal cramps | 1 | - | - |
| Edema | 1 | - | - |
| Myalgia | 1 | - | - |
| Fatigue | 4 | 1 | - |
| Chills | 3 | - | - |
| Pain, other | 1 | - | - |
| **WORST DEGREE** | **18** | **7** | **2** |
| **Supplemental genitourinary toxicity type** | | | |
| Incontinence | 2 | 2 | 1 |
| Dysuria | 7 | 7 | 3 |
| Urinary retention | 2 | - | - |
| Increased frequency/ urgency | 9 | 11 | 2 |
| Hemorrhagic cystitis | - | 1 | - |
| Bladder cramps | 1 | 3 | - |
| Bladder-other | 3 | 4 | - |

| | N=45 Grade | | |
|---|---|---|---|
| | 1 (n) | 2 (n) | 3 (n) |
| Renal failure | - | - | - |
| Renal-other | - | - | - |
| Ureteral obstruction | - | - | - |
| GU fistula | - | - | - |
| GU-other | 3 | 2 | 1 |
| **WORST DEGREE** | **13** | **16** | **5** |

**Table 3**

Best overall response and recurrence-free rate

| **Response** | **TCC Patients** | | **CIS ± TCC Patients** | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| Complete response | 9 | 42.9 | 5 | 23.8 |
| Treatment Failure | 10 | 47.6 | 16 | 76.2 |
| Unevaluable* | 2 | 9.5 | 0 | 0 |
| Total | 21 | | 21 | |
| **Recurrence-free rate** | **TCC Patients (N=21)** | | **CIS ± TCC Patients (N=5**)** | |
| | Rate | 90% CI | Rate | 90% CI |
| 12 months | 20% | 7.8%–36.1% | 80% | 31.4%–95.8% |
| 24 months | 15% | 4.9%–30.2% | 80% | 31.4%–95.8% |
| **Median time to recurrence** | **TCC Patients (N=21)** | | **CIS ± TCC Patients (N=5**)** | |
| | 5.3 months | | 37.3 months | |

CIS, carcinoma in situ; TCC, urothelial carcinoma (formerly transitional cell carcinoma)

*Reasons patients were unevaluable: Patients could not tolerate protocol therapy and were off study on the first day of treatment

**only CIS patients with CR are included