# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-892

## MEDICAL REVIEW(S)

# FDA MEDICAL OFFICER REPORT FOR ODAC
## For the September 1st, 1998 Meeting of the Oncologic Drugs Advisory Committee

## AD-32 (VALSTAR) NDA#20-892

# MEDICAL OFFICER REVIEW

**NDA#20-892 TITLE: AD-32 (Valsar) for the Treatment of BCG Refractory Carcinoma in situ of the Urinary bladder in a selective patient subset.**

**SPONSOR : ANTHRA PHARMACEUTICALS INC.**

## 1. SUMMARY OF SPONSOR'S PREVIOUS SUBMISSION OF AD-32 (Valrubicin)

AD-32 is a semisynthetic highly lipophylic analog of the anthracycline antibiotic doxorubicin proposed for intravesical use in the treatment of patients with biopsy-proven carcinoma in situ (CIS) of the bladder who are refractory to BCG immunotherapy. On December 31,1997, under the trade name Valrubicin, the sponsor submitted to the FDA , results of two studies (A9301 and A 9302) utilizing AD-32 in the treatment of 90 patients at 41 centers by 43 investigators for the stated indication. The results were presented at the Oncology Drug Advisory Committee (ODAC) meeting on June 1st , 1998. The sponsor provided evidence to support complete responses in 19 of the 90 patients treated with AD-32 for this indication. The Agency presented the results of its review of the data submitted. The FDA determined that there were 7 definite responses out of the 90 treated patients, with 7 questionable responders. ODAC members voted unanimously not to approve AD-32. With 11 negative votes , 1 abstention and no positive votes, the committee members indicated that the benefit of AD-32 in BCG-refractory CIS patients had not been demonstrated. Furthermore, considering that a large number of patients (at least 71 of 90 patients) were unresponsive to this therapy, the committee was concerned about the potential risk to patients from delaying cystectomy in order to give intravesical AD-32 treatment.

An eleven point proposal was submitted to the Agency for discussion at a meeting on June 19th, 1998. These points were discussed, but the Agency remained unconvinced that AD-32 had been demonstrated to be safe and effective. However, the Agency recognized the possibility that safety and efficacy might be demonstrable in a subset of patients for whom cystectomy was medically contraindicated. Anthra was to provide additional data that a defined population of CIS patients exists who are BCG refractory, but for whom cystectomy was medically contraindicated. Literature-based evidence defining contraindications to surgery was to be provided as well. If a sizable number of such patients could be convincingly demonstrated to exist, this might constitute an approvable basis for the drug. The Agency also expressed interest in the sponsor's suggestion concerning the need to re-evaluate patients who were protocol classified by Anthra as No

CR due to recurrence with only Ta G1/G2 disease. By reviewing this category of patients, it may be possible to increase the number of patients who are classified as CRs. The applicant excluded this group of patients from the CR category in its original protocol. Anthra subsequently submitted a major amendment to the NDA to address whether AD-32 might be approvable for patients who are not candidates for cystectomy.

This submission extended the regulatory clock by three months and provided the sponsor another opportunity for its amended application to be discussed at a subsequent ODAC meeting.

## II. VALSTAR (VALRUBICIN): PROPOSED INDICATION:

The NDA is resubmitted under a new trade name, Valstar, with an amended proposed indication and usage:

## III. DOCUMENTS REVIEWED:

Case Summaries of Responders, Vol. 1.40-1.44 received December 1997
Tables and Reports of Individual Treatment Studies Vol.1.33
Pre-meeting package dated June 11,1998
Major Amendment Vol. 2.1 received June 29,1998
Amendment No.27 received July 28,1998.
Amendment No28 received July 31,1998

## IV. NEW ANALYSES

Anthra's five main points in support of use of valstar and for reconsideration of an approvable basis for AD-32.
FDA responses follow each argument

### A) PATIENTS WHO ARE NOT CANDIDATES FOR SURGERY

If a significant subpopulation of BCG refractory CIS patients exists who are not candidates for cystectomy due to medical contraindications or patient refusal, they might represent a population for whom AD-32 treatment could be considered safe and effective. The sponsor provides the following criteria as indicators of surgical risk, hence medical contraindication to cystectomy:

- Age >75 years
- Age >75 years with or without a history of cardiovascular or pulmonary disease.
- History of cardiovascular or pulmonary disease plus other types of cancer.

The table below represents data on 16 patients who were enrolled in the study but according to the applicant, are not candidates for radical cystectomy based on the criteria indicated above. 4 of the 16 patients (25%) are in the applicant's classified group of complete responders on valrubicin therapy, while 2 of the 16 patients ( 12.5%) are in the FDA's group of responders.

TABLE 5

| Characteristic(s) | Specific Condition(s) | N | Patient Numbers[a] |
|---|---|---|---|
| Age ≥75 yr | 75-82 yr | 4 | |
| Age ≥75 yr + History or development of cardiovascular or pulmonary disease | TIA, COPD, CVA, MI | 2 | |
| History or development of cardiovascular disease | TIA, CAD, CABG, MI, angioplasty | 5 | |
| History or development of pulmonary disease | ARDS, emphysema, sclerosing procedure to lung | 3 | |
| History of cardiovascular or pulmonary disease + other type of cancer | COPD and lung cancer; CAD, MI, and renal cancer | 2 | |

[a] Suffix "R" after a patient number identifies a CR.
[b] Patient died of myocardial infarction 2 months after clinical failure.

**Literature Review:**

The sponsor provides literature documentation to support the position and criteria outlined in the table above. The arguments can be summarized as follows:

Bladder cancer is largely a disease of older people, median age at presentation is between 65 and 70 years, and the incidence increases with age. A large percentage of patients undergoing treatment for bladder cancer therefore have multiple comorbid conditions. Since smoking is a major etiologic factor for development of bladder cancer, pulmonary and cardiovascular diseases further complicate the clinical competence of these elderly patients to withstand such an arduous procedure as radical cystectomy

Radical cystectomy involves extensive removal of organs and tissue in both male and female patients. The procedure usually takes 6 to10 hours to complete, resulting in. large fluid shifts and other hemodynamic complications. Radical cystectomy therefore meets the criteria of high risk noncardiac surgery as defined by the American College of Cardiology/American Heart Association Task Force Guidelines.

The overall mortality from cystectomy is 2.5%. In elderly patients, the mortality is higher (3% to6%) than in younger patients(1%to3%).(Skinner et.al.)

Coexistence of multiple risk factors greatly increase the risk of surgical complications and operative mortality. These factors include: Age, cardiovascular function, pulmonary function, hepatic function and nutritional status. Pre-operative nutritional status is not uncommonly poor in elderly patients.

**Patient refusal of Cystectomy**

In the latest amendment submitted July 30th 1998, the sponsor provides clinical notes of investigators indicating patient refusal of cystectomy when offered this treatment option after failure of intravesical therapy of CIS. The sponsor considers patient refusal of cystectomy an acceptable indication for valrubicin (valstar).

**FDA RESPONSE**

The sponsor lists a group of sixteen patients who are not considered to be candidates for medical reasons. The response rates to valrubicin therapy as judged by both the sponsor, 4 of 16 (25%) and the FDA, 2 of 16 (12.5%) are similar to the rates in the total population of patients studied, 21% and 8% respectively. Hence this is not a unique group of patients, but appears to be a representative sample of the population of patients in the study.
Two patients in this group have successfully undergone radical cystectomy since this list of patients was compiled. Both patients had deep muscle invasive disease at cystectomy (pT3b/pTis). Both patients are over age 75 years.

**Literature Review :**

The literature is replete with information on radical cystectomy in elderly patients.(Ref 1-14) A preponderance of the information advocates the need for cystectomy in this population of patients. Surgery can be performed with acceptable morbidity and mortality if meticulous attention is paid to the pre and postoperative needs of the patient.
The following represents samples of conclusions of many of the articles. Some of the articles were included in the sponsor's submission. These articles directly respond to all of the concerns raised by the sponsor regarding radical cystectomy in this patient population.

"Patients in their eighth decade are becoming an increasingly important group numerically in the practice of uro-oncology, and it will be necessary to develop more sophisticated and flexible approaches for their management. Provided that care is taken to plan for their altered physiologic requirements. it is clear that comparable (or better) outcomes can be anticipated from well-designed treatment programs that involve surgery, radiation or chemotherapy, applied as single modalities or in combination.....Advanced age alone should not preclude the provision of active and effective strategies of treatment." (Skinner E, Raghavan D, et.al Ref 1 page312)

"Elderly patients have increased risk from urologic surgery, mostly owing to associated comorbid factors. They are also a population that can benefit greatly from surgery...Most of this increased risk can be anticipated and managed so that surgery is safe....With effective pre and postoperative care the risks are minimized, the probability of a successful outcome is maximized, and the quality of life is improved for most."(Smith,R, Osterweil D, et.al. Ref 2 page 40)

"The treatment goal in any cancer surgery is to cure the primary neoplasm and preserve quality of life. We believe these can best be achieved by cystectomy for invasive bladder cancer even in the 80 year old patient. Conservative or alternative strategies often result in

progressive, uncontrolled pelvic cancer which is associated with bleeding, pain, disability obstipation and repeated bladder manipulations. Frequent hospitalizations for months or years until death are often required unless the local bladder tumor is definitively treated..... Radical cystectomy in this population offers the best opportunity for sustained disease free quality survival."(Strumbakis N, Herr HW, Ref 3)

"...radical cystectomy is a relatively safe procedure for elderly patients with invasive transitional cell carcinoma of the urinary bladder. ...The insignificant increase in the operative risk in older patients is by far less than the major effects of alternative treatment and the associated morbidity and mortality. Death related to under treated cancer is much more common than death related to intercurrent medical diseases, and the quality of life during survival is strongly affected. Thus , the elderly patient who is found unsuitable for surgery is deprived not only of his right to definitive curative therapy but also is exposed to significantly higher morbidity and mortality and worse quality of life than are patients who undergo operations." (Ref 7)

**Patient Refusal of Cystectomy**

The choice of therapy for a disease should be determined by science-based evidence of safety and efficacy of that particular therapy. These are the issues under consideration for determininig approvability of valrubicin for use in patients with CIS bladder cancer who have failed BCG treatment. Patient refusal to accept the recommedation for indicated therapy of any disease usually calls for better patient education about the disease. Urologic oncology is no exception to this medical dictum. As emphasized by Skinner, "Given the potential for successful outcomes of treatment, we must place greater emphasis on educating the elderly about the symptoms of bladder cancer, encouraging them to present as early as possible, thus facilitating the best possible results of treatment."(1).

## B) RESPONSE TO INTRAVESICAL TREATMENT IN COMPLETE RESPONDERS:

The applicant suggests that use of intravesical AD-32 changed the course of the disease in the 19 patients claimed by Anthra to be complete responders (CR). This is demonstrated by comparing an individual's duration of response on AD32 treatment duration of response to prior therapy received by the same patient. Figure 1 purports to demonstrate that "a statistically significant difference" exists between the response to valrubicin therapy and the response to each of the previous three treatment regimens received by the patient. The same information is also presented as scatter plots in which response to valrubicin therapy is compared to the last intravesical therapy of any kind or to BCG.

FIGURE 1
Response to Prior Intravesical Therapies Versus Response to Valrubicin in CRs (N=19)

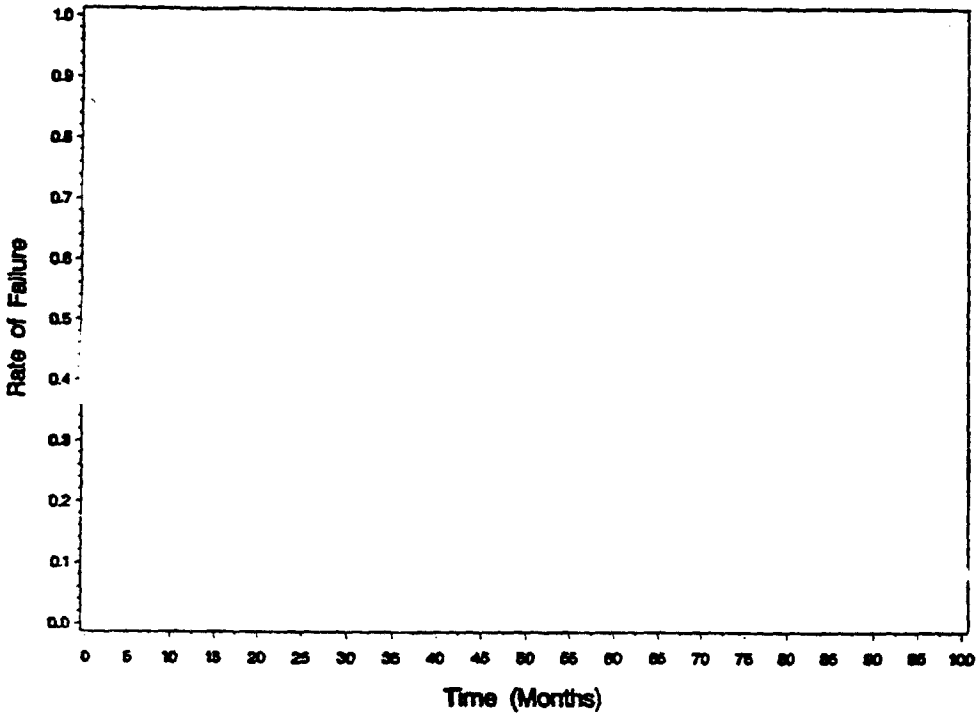


FIGURE 2

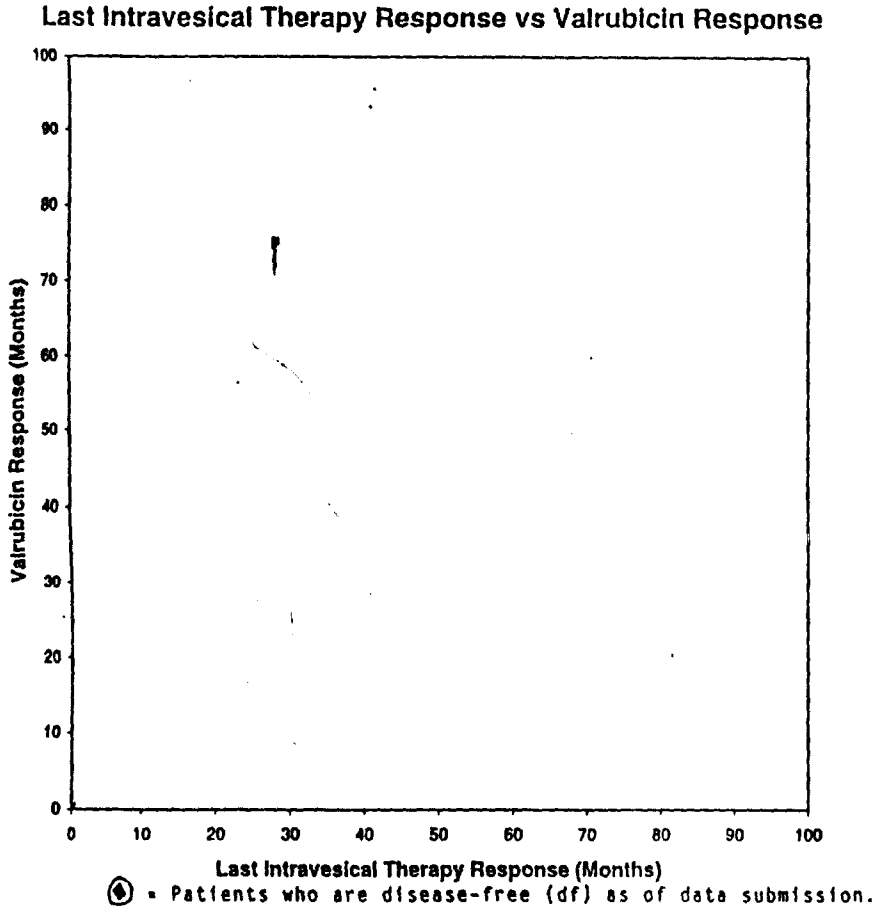
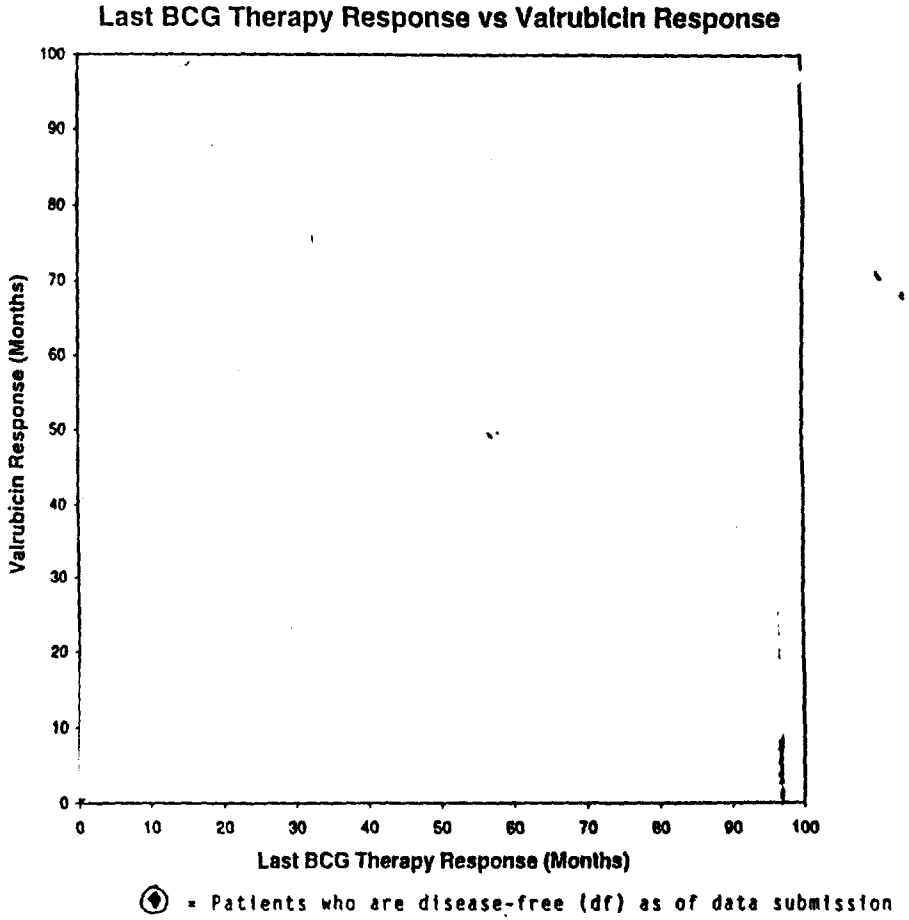



FIGURE 3



**FDA RESPONSE**

See the statistical review by Gang Chen Ph.D for more details. ——

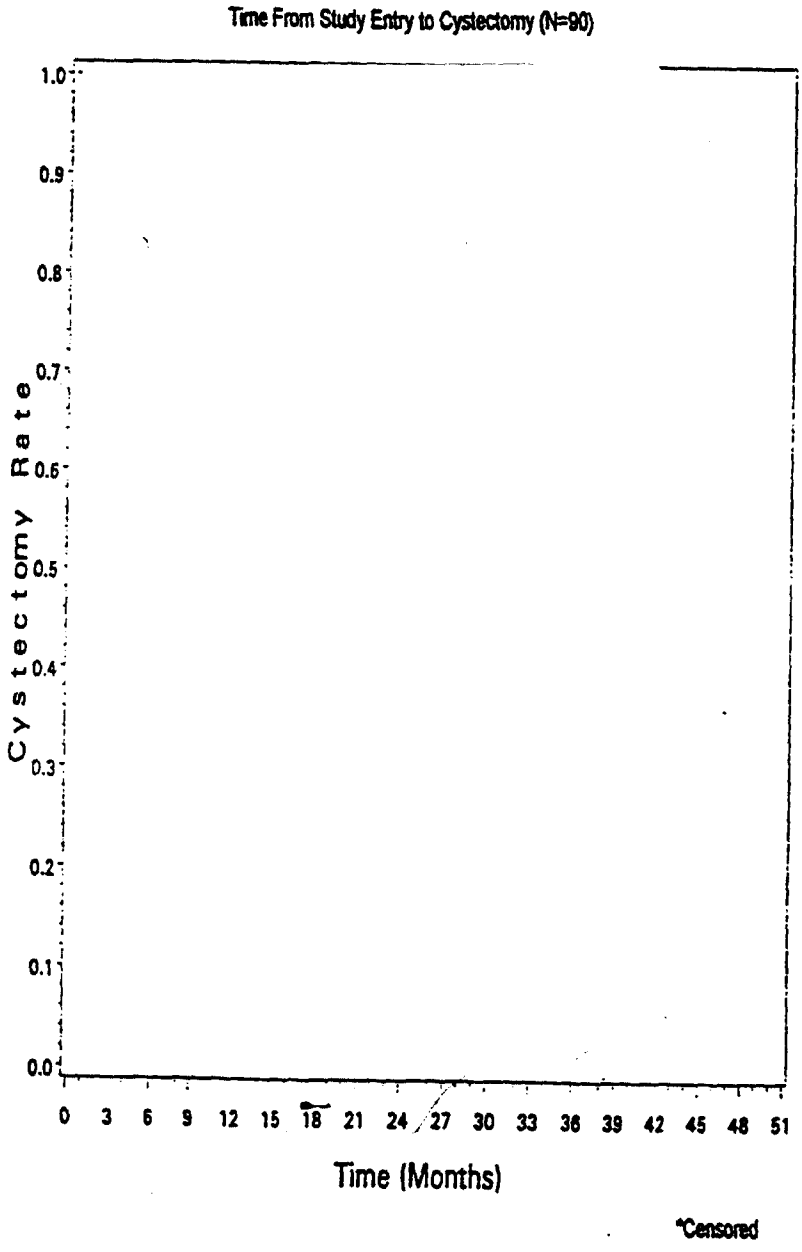
The Agency did show in its review of the original submission that 7 of the 90 patients who received intravesical AD-32 treatment had obvious complete responses. The time to recurrence in this group of patients ranged from months. This small group of patients therefore did derive benefit from the treatment received by delaying cystectomy. There were 7 others in whom responses were possible, but such responses were not strictly documented. These differences in the Agency's number of CR patients and the duration of the CRs naturally affect the analysis of the data presented by the applicant.

Given this caveat, data presented by the applicant giving an analysis of duration of response to prior intravesical therapies versus response to valrubicin would suggest that CR patients were disease free longer on AD-32 therapy than with prior intravesical treatments. The Kaplan Meier plots provided are exploratory, but do show a trend in favor of AD 32 treatment. The scatter plots can be interpreted as yielding the same conclusion. Statistical significance cannot, however. be determined from the data presented and the *p-value* is uninterpretable, since this is a retrospective, non-randomized analysis.

The log-rank test is invalid because of the dependent structure of the groups of data being compared. A test statistic based on paired or matched data analysis would have been more appropriate. The scatter plot evaluates only claimed CRs: 19 of 90 patients selected for good outcomes. A scatter plot of all 90 patients might not appear so asymmetric.

**C) TIME TO CYSTECTOMY IN RESPONDERS VERSUS NON- RESPONDERS:**
The applicant provides Kaplan-Meier analysis of time to cystectomy in the 19 CRs and 71 non CRs in which a claim of "statistically significant difference" is shown between the two groups. A median time to cystectomy of 25.3 months is claimed for non-responders, while the median time for responders "has not yet been reached." The applicant thus implies that improvement in time to a negative event, in this case cystectomy, is a benefit that should be viewed as a positive effect of AD-32 treatment.

FIGURE 2



**FDA RESPONSE**

The Kaplan-Meier analysis of time to cystectomy provided by the sponsor on the entire population of 90 patients in the study does suggest an association between CR status and time to cystectomy. However, an association between response and time to cystectomy does not prove that AD-32 was responsible for the response or delay in cystectomy. One must also be confident that the observed "responses" were legitimate and would not have been observed even without intravesical therapy. It is quite possible that patients with less aggressive disease are both more likely to respond to therapy-related manipulations (TUR) and also are less likely to undergo cystectomy even without AD-32 treatment.

**D) HOMOGENEITY OF THE POPULATION:**

The sponsor attempts to show that patients in the CR group do not represent a favorable class, but are similar in baseline and demographic characteristics to the non-CR patients. The accompanying table represents demographic and baseline characteristics of the patients in each group.

Table 1. Comparison of Demographic and Baseline Characteristics

| | All (N=90) | CRs (N=19) | Nonresponders (N=71) |
|---|---|---|---|
| Male | 88% | 89% | 87% |
| White | 98% | 100% | 97% |
| 60-79 yr | 79% | 95% | 75% |
| Median duration of transitional cell carcinoma[a] | 3.3 yr | 3.3 yr | 3.4 yr |
| Median duration of Tis[a] | 25 mo | 28 mo | 24 mo |
| Baseline local bladder symptoms | 50% | 68% | 45% |
| ≥2 Prior BCG | 70% | 68% | 70% |
| Last BCG ≤3 mo before study entry | 2% | 5% | 1% |
| Last BCG >3–24 mo before study entry | 73% | 68% | 75% |
| Cytology (+) at baseline | 63% | 58% | 65% |
| ≥2 (+) biopsy sites at baseline | 53% | 47% | 55% |
| History of ≥2 (+) biopsy sites | Not done | 89% | Not done |
| Two sites (+) for Tis at baseline and (+) cytology | 38% | 32% | 39% |
| Received intravesical tx after failure/recurrence | 37% | 37% | 37% |

[a] Time from initial diagnosis to study entry.

The sponsor implies that the natural history of the disease as well as prior intravesical therapy was not different in either category of patients.

**FDA RESPONSE**

Demographic and baseline data appear reasonably balanced between Responders and Non-Responders. The BCG information however suggests that more patients in the CR group could potentially still be BCG responsive, since 5% of CR patients versus 1% of Non responders had their last BCG treatment ≤ 3months before study entry.

## E) CLINICAL BENEFIT (CB)

The sponsor proposes the use of change in clinical profile of disease as an indicator of clinical benefit (CB) rather than the CR (complete response) criteria utilized in the protocol. Through this mechanism, the sponsor proposes to add 10 more patients to the group of patients who derived benefit from AD-32 treatment. These 10 patients failed valrubicin therapy with low grade papillary tumors only (stage Ta, grade 1 or 2 ) and might have had their response category upstaged to this more favorable category to indicate lack of recurrence of CIS.

As a result of this reclassification, the sponsor claims 29 CB and 61 non CB patients, as opposed to 19 CR and 71 non CR patients. The table below includes the sponsor's list of 10 additional patients who failed with TaG1 or TaG2 disease, and the claimed duration of benefit on therapy.

Table 2. Patients With Clinical Benefit

| COMPLETE RESPONDERS | | PATIENTS WHO FAILED WITH TaG1 OR TaG2 | |
|---|---|---|---|
| *Anthra Patient ID (FDA Patient Number)* | *Time to Failure or Last Follow-up (months)*[a] | *Anthra Patient ID* | *Time to >TaG2 or Last Follow-up (months)*[b] |
| | 15 | | 9 |
| | 24 | | 19 |
| | 15+ | | 27[c] |
| | 24+ | | 8 |
| | 21 | | 6+ |
| | 12 | | 10[c] |
| | 27+ | | 17+ |
| | 18 | | 20 |
| | 36 | | 3+ |
| | 24+ | | 34+ |
| | 21+ | | |
| | 21+ | | |
| | 18 | | |
| | 12 | | |
| | 21+ | | |
| | 9 | | |
| | 9 | | |
| | 9 | | |
| | 9 | | |

[a] A "+" indicates that the patient was still disease-free at the month shown, which was the time of the last follow-up.
[b] A "+" indicates that, at the time indicated, the patient still had TaG1 or TaG2 disease and no further biopsy data are available.
[c] Based on date of cystectomy. Patient had no evidence of disease >TaG2 before cystectomy.

### Time to cystectomy as a measure of clinical benefit.

Time to cystectomy (TTC) is also used to further characterize CB and CR patients. In CB patients, TTC is "significantly different" in CB from that in the non-CB patients, as it is in CR versus non-CR patients. A larger difference is claimed in CB and non CB patients, in comparison with CR and non CR patients. The sponsor therefore believes that CB should be a better measure of efficacy of AD-32 than CR.

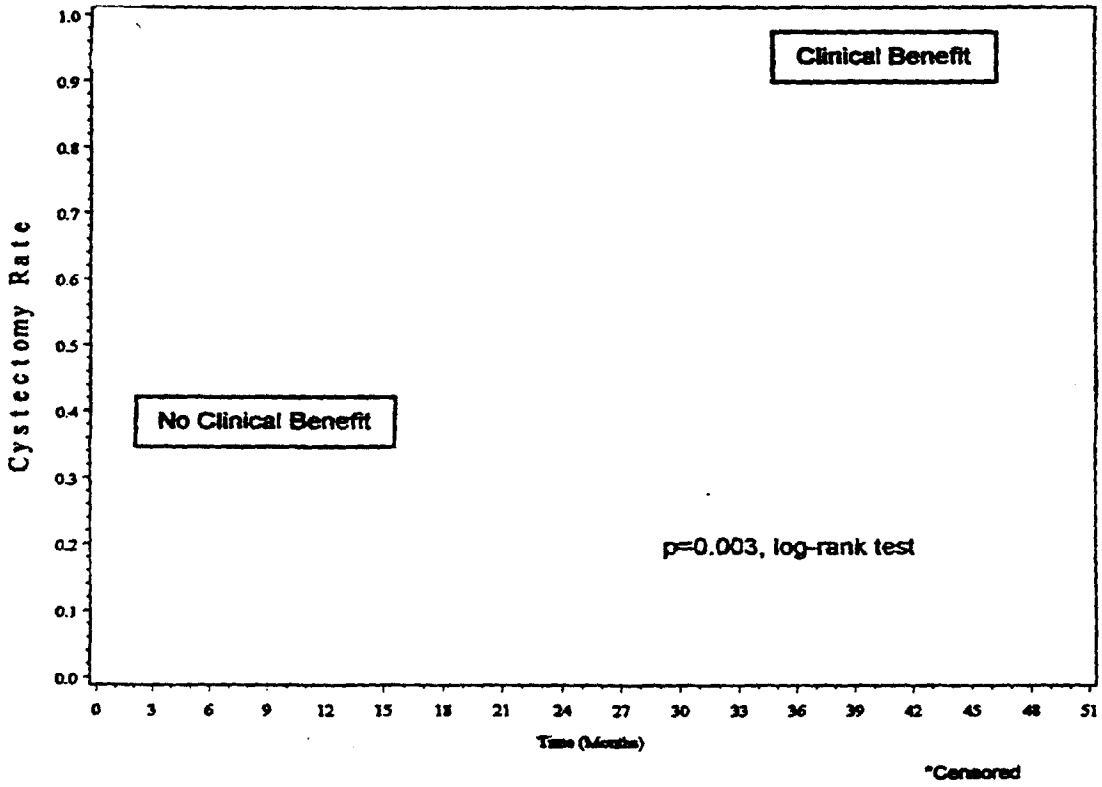
In June,1998, 37 of 90 patients had undergone cystectomy, for a cystectomy rate of 41%. 7 additional patients had undergone cystectomy since June 1st. 1998 (6 radical cystectomy and 1 partial cystectomy). The total cystectomy rate is most recently 44 of 90 patients

(49%) Three of the seven patients were found to have advanced pathologic disease (T3) at cystectomy. One additional patient has died due to advanced bladder cancer.
The figure below represents the sponsor's graphic representation of cystectomy rate over time in CB versus non CB patients. The updated figure for the 44 patients is similar to that for the 37 patients cystectomized by December 31,1997.

On the basis of increased cystectomy rate and increased time to cystectomy for patients with CR, the applicant believes that CB should be a better measure of efficacy of AD-32 than CR.

**The data that were used to generate this analysis were included in the Access database submitted to the FDA as part of Minor Amendment 16 (April 29, 1998).**

FIGURE 6
Time to Cystectomy for Patients With Clinical Benefit (N=29) and Patients Without Clinical Benefit (N=61)



**FDA RESPONSE**

The Agency's response is divided into three sections:

1. The sponsor's 10 additional patients who failed with TaGI or TaG2 lesions.

2. The FDA re-analysis of the 19 CR patients claimed by the sponsor, to determine if the Agency's count of responders or duration of response could be readjusted based on this re-classifying Ta G1/G2 relapses.

3. Use of Clinical Benefit (CB) rather than Complete Response (CR) as a clinical evaluation end point.

1) Data on the 10 patients as presented in the Clinical Data Section Vol. 33. Patient Efficacy Profile are shown in the accompanying tables:
The 10 patients are presented in two categories, 1 and 2:

**Category 1 Patients: #s**

This category of patients could conceivably be considered for response if collected data were more complete. However with data available for review these cases cannot be classified as responses.
The required information which the sponsor has been requested to provide, if available, include:

- Historical data documenting duration of TCC including CIS
- Prior intravesical therapy including BCG
- Were these patients BCG failures prior to study entry?
- What is the duration of follow up post PDE in 3 patients
  and post 6 months in 2 patients
- Pathologic documentation of Tis and Ta.

In the absence of these data it is difficult to validate the response duration ranging from 3+ months to 34+ months reported by the sponsor in this group of patients.

**Category 2 Patients #s**

This category of patients can not conceivably be considered for response for the following reasons:
In addition to the deficiencies listed above in category 1;

- All patients had positive cytology at PDE, 3 months after study entry. This suggests existence of disease of a greater import,either missed in the bladder or present in extravesical areas such as the ureters or prostatic urethra. Ta lesions are not usually associated with positive urine cytology.
- Patient had positive urine cytology both at baseline and at PDE with no Ta lesions. There is no follow up urine cytology or biopsy report provided.

For these reasons, this reviewer believes that the applicant has not provided convincing evidence that will support the addition of 10 more patients to the response category.

## Summary Table 3: Patient Effic rofile - A9301/A9302/A9303

| ent: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 1 | 07/28/94 | NED | | | | | Tis | | | | NED | | | | 07/28/94 | Susp | 08/12/94 | - |
| PDE | 12 | 12/28/94 | NED | NED | NED | | | | NED | | | NED | NED | | | 12/28/94 | Neg | 12/27/94 | - |
| 6 Months | 13 | 03/28/95 | Ta | NED | NED | | | | NED | | | NED | NED | | | 03/28/95 | Neg | 04/03/95 | - |

## Summary Table 3: Patient Efficacy Profile - A9301/A9302/A9303

| Patient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 1 | 04/05/95 | | | | | | | | | | Tis | | | | 04/04/95 | Susp | 04/14/95 | - |
| PDE | 12 | Not Done | | | | | | | | | | | | | | Not Done | | 08/07/95 | - |
| 6 Months | 13 | 01/26/96 | | | | Ta | Ta | | | | | | | | | 01/26/96 | Pos | 01/19/96 | - |

## Summary Table 3: Patient Efficacy Profile - A9301/A9302/A9303

| atient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 1 | 06/21/95 | | NED | | | | | | | Tis | | NED | | | 06/21/95 | Susp | 08/11/95 | + |
| PDE | 12 | 11/08/95 | NED | NED | NED | | | | | | Ta | | Ta | | | 11/08/95 | Susp | 11/08/95 | - |

## Summary Table 3: Patient Efficacy Profile - A9301/A9302/A9303

| Patient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 1 | 08/21/96 | Tis | | | | | | | | | | | | | 08/21/96 | Susp | 08/21/96 | + |
| PDE | 12 | 11/20/96 | Ta | NED | | | | | | | | NED | NED | | | 11/20/96 | Susp | 11/20/96 | - |

## Summary Table 3: Patient Efficacy Profile - A9301/A9302/A9303

| atient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 1 | 11/11/94 | | NED | NED | | | | NED | | NED | Tis | NED | | | 11/11/94 | Neg | 11/11/94 | - |
| PDE | 12 | 06/19/95 | | NED | Ta | | | | | | NED | Ta | NED | NED | | 06/19/95 | Pos | 06/19/95 | - |

## Summary Table 3: Patient Efficacy Profile - A9301/A9302/A9303

| Patient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage: PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 1 | 11/04/94 | | Tis | | | | | | | | | | | | 11/04/94 | Susp | 11/04/94 | + |
| PDE | 12 | 02/23/95 | NED | NED | NED | | | | NED | | | NED | NED | | | 02/23/95 | Neg | 02/22/95 | + |

## Summary Table 3: Patient Efficacy Profile - A9301/A9302/A9303

| Patient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage: PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 1 | 10/19/94 | | | | | | | Tis | | | | | | | 10/19/94 | Susp | 01/20/95 | + |
| PDE | 12 | 04/10/95 | Ta | | | | | | NED | | | | | | | 04/10/95 | Susp | 04/05/95 | + |

## Summary Table 3: Patient Efficacy Profile - A9301/A9302/A9303

| Patient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage: PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 1 | 01/30/95 | | | | | | Tis | | | | | | | | 01/30/95 | Susp | 01/30/95 | + |
| PDE | 12 | 05/31/95 | | NED | NED | | | | | | | NED | Ta | | | 05/31/95 | Neg | 05/31/95 | + |

## Summary Table 3: Patient Efficacy Profile - A9301/A9302/A9303

| Patient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage: PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline | 1 | 01/17/95 | | | | | | Tis | | | | Tis | | | | 01/17/95 | Neg | 02/03/95 | - |
| PDE | 12 | 06/08/95 | | | | | | NED | | | Ta | | | | | 06/08/95 | Susp | 06/08/95 | + |

2) Agency's re-analysis of its CR status:
A review of the records reveal 3 patients classified by the applicant but not by the FDA as CR (FDA#s 4, 10 and 18) that could be considered for re-analysis of findings based on failure due to TaG1/G2 lesions. The results of these patients are given as presented in the sponsor's summary table of Patient Efficacy Profile. The results of FDA re-analysis of the data are presented in the table below.

| FDA PATIENT # (ANTHRA #) | FDA FINDINGS |
|---|---|
| | At 18 mos. has positive Urine cytology along with **Ta** lesion. Subsequent Urine cytology results are not available |
| | Failed at 6 months due to positive Urine cytology prior to **Ta G2and Tis** lesions at 7 months |
| | Failed at 9 months due to positive Urine cytology prior to **Ta G1-2** lesion at 12 months Urine cytology was not repeated at 12 months. |

In none of these patient does a designation of CR seem appropriate. These findings show that failure with Ta G1/G2 disease does not alter the Agency's original findings.

## Summary Table 3: Patient Efficacy Profile - A9302

| Patient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage: PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Historical | 0.01 | 05/20/92 | | | | | | | | | | | Ta | | | | | NAV | |
| Historical | 0.02 | 07/30/92 | | | Tis | | | | | | | | | | | | | | |
| Historical | 0.03 | 06/23/93 | | | | | | | | | | | | | TCC/Tis | | | | |
| Historical | 0.04 | 05/02/94 | | | | | | | | | | | | | TCC/Tis | | | | |
| Baseline | 1 | 05/26/94 | Tis | NED | NED | | | | NED | | NED | NED | NED | | | 05/26/94 | Other | 05/26/94 | + |
| PDE | 12 | 08/30/94 | NED | | | | | | | | | | | | | 08/30/94 | Neg | 08/30/94 | - |
| 6 Months | 13 | 01/10/95 | NAV | | | | | | | | | | | | | 12/05/94 | Neg | 12/05/94 | - |
| 9 Months | 14 | NAP | | | | | | | | | | | | | | Not Done | | Not Done | |
| 12 Months | 15 | 06/13/95 | NED | | | | | | | | | | | | | 06/13/95 | Neg | 06/08/95 | - |
| 15 Months | 16 | NAP | | | | | | | | | | | | | | 10/30/95 | Neg | 10/30/95 | - |
| 18 Months | 17 | 03/14/96 | SevD | | | | | | | | Ta | | NED | | | 02/19/96 | Susp | 02/19/96 | + |

## Summary Table 3: Patient Efficacy Profile - A9302

| Patient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage: PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Historical | 0.01 | 10/14/91 | | Ta | | | | | | | | | | | | | | 01/16/92 | - |
| Historical | 0.02 | 04/22/92 | | | | | | | | | | | TCC | | | | | | |
| Historical | 0.03 | 07/17/92 | | | | | | | | | | | | | Tis | | | | |
| Historical | 0.04 | 07/12/93 | | | | | | TCC | | | | | | | Tis | | | | |
| Baseline | 1 | 10/11/94 | Ta | | | | | | | | | | | | | 10/11/94 | Pos | 11/02/94 | - |
| PDE | 12 | 03/08/95 | NED | NED | NED | | | | | | | NED | NED | | | 03/08/95 | Pos | 03/08/95 | - |
| 6 Months | 13 | 06/07/95 | NED | NED | NED | | | | | | NED | NED | NED | | | 06/07/95 | Unk | 06/06/95 | - |
| 9 Months | 14 | 09/20/95 | NED | NED | NED | | | | | | NED | NED | NED | | | 09/20/95 | Other | 09/20/95 | + |
| 12 Months | 15 | 01/03/96 | NED | SevD | NED | | | | | | SevD | Ta | NED | | | 12/13/95 | Pos | Not Done | |

## Summary Table 3: Patient Efficacy Profile - A9301

| Patient: Evaluation | Visit | Biopsy Date | Biopsy Site & Tumor Stage: PW | RW | LW | RU | LU | N | PU | U | AW | TR | D | PS | Un-specified* | Cystoscopy Date | Cystoscopy Result | Cytology Date | Cytology Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Historical | 0.01 | 09/04/92 | | | | | | | | | | | | | Ti | | | NAV | |
| Historical | 0.02 | 01/22/93 | | | | | | | | | | | | | Ta | | | | |
| Historical | 0.03 | 07/02/93 | | | | | | | | | | | | | Ta | | | | |
| Historical | 0.04 | 11/03/93 | | | | | | | | | | | | | Ti | | | | |
| Historical | 0.05 | 02/25/94 | | | | | | | | | | Ta | Tis/Ta | | | | | | |
| Historical | 0.06 | 05/03/94 | Ta | | | | | | | | | | | | | | | | |
| Historical | 0.07 | 10/06/94 | | | | | | Tis | | | | | Ta | | | | | | |
| Historical | 0.08 | 07/11/95 | | | Ta | Tis | | Ta | | | | Ta | | | | | | | |
| Historical | 0.09 | 08/29/95 | | | | | | Ta | | | | | | | | | | | |
| Baseline | 1 | 03/14/96 | NED | NED | Tis | | Ta | | NED | | | Ta | | | | | | 04/16/96 | - |
| PDE | 12 | 07/25/96 | | NED | NED | | | | | | | NED | NED | NED | | 07/25/96 | Neg | 07/25/96 | - |
| 6 Months | 13 | 10/25/96 | NED | NED | NED | | | | NED | | | NED | NED | NED | | 10/25/96 | Unk | 10/25/96 | + |
| 9 Months | 14 | 11/25/96 | Ta | | Tis | | | | | | | | | | | 11/25/96 | Pos | Not Done | |

3) Clinical Benefit as a better determinant of surrogate end point than Complete Response: The sponsor provides data to support the view that CB is a more valid measure of patient benefit in this disease than time to clinical failure (CR). Kaplan Meier analysis of the data for cystectomized versus non cystectomized patients are presented for pre and post ODAC cut off dates, and the results are similar. The curves are similar to that for complete response (CR) and again are considered by the Agency as exploratory.

The conclusion that Kaplan Meier analyses show CB to be a more appropriate measure of end point is questionable. Complete Response of adequate duration remains a useful end point for new drug approval in an appropriate population of patients with CIS in whom cystectomy is required. The efficacy outcome of a trial utilizing such an end point in a single arm-trial should be impressive and unequivocal considering the risk of delaying cystectomy.

The time to cystectomy figure provided along with the updated information on cystctomized versus non-cystectomized patients suggests that there is a total of 6 patients with advanced bladder cancer (T3) and no deaths among the 44 cystectomized patients. There are however 5 deaths due to bladder cancer among the 46 non-cystectomized patients.

# V SUMMARY AND CONCLUSION.

Anthra Pharmaceuticals Inc. has resubmitted a major amendment to its original NDA application for the intravesical use of AD-32 (Valrubicin/Valstar) for the treatment of patients with carcinoma-in-situ of the bladder who are refractory to BCG. The members of the Oncology Drug Advisory Committee (ODAC), at a recent meeting on the application and by a unanimous vote, were unconvinced about the safety and efficacy of AD-32 for the claimed indication. This amendment represents the sponsor's effort to show that there exists a population of patients who are not candidates for cystectomy due to medical contraindication or patient refusal, and that this population represents a suitable group for whom AD-32 is a safe and effective treatment.
The data presented by the applicant however, have failed to show that a special population of patients exists for whom surgery is contraindicated. On the contrary, literature-based evidence, including that supplied by the applicant, encourages early cystectomy in patients who fail intravesical therapy in this disease, regardless of age. With appropriate pre and post operative care the comorbid medical problems that prevail in this elderly population of patients can be ameliorated. Patient refusal to accept cystectomy calls for education of the patient concerning the risks of progressive and metastatic bladder cancer or even death if cystectomy is delayed in patients who have failed multiple intravesical therapy.

The sponsor has demonstrated that patients who responded to valrubicin were disease-free longer on AD-32 than on their previous intravesical therapies. However, given the small number of patients involved (nineteen), and the exploratory , retrospective nature of the analysis, the importance of this finding is less clear.

The applicant has also demonstrated an association between CR status and time to cystectomy. Again, the sample size is small and the conclusions one could draw vis-a -vis the contribution of AD-32 treatment to this finding is questionable.

The population of patients in the study appears homogenous, with similar demographic and baseline data among responding and non-responding patients.

The sponsor has failed to show that there are additional patients who can be added to the complete response category through a broadening of the criteria to include Ta G1/2 patients. Similarly, the Agency has been unable to identify additional patients from the 19 CRs that the applicant claims, who could qualify for inclusion in the CR category.

The data submitted do not support the view that any endpoint other than durable Complete Response is a more appropriate measure of clinical benefit in this disease.

FDA analysis can only document that valrubicin benefits only a small minority of patients (8%-14%). More convincing however, are data showing that early cystectomy saves lives and prevents disseminated disease in non-responsive patients or patients who recur following response to drug therapy. Mortality rate due to bladder cancer is zero in 44 cystectomized

patients and 11% ( five of 46) in uncystectomized patients. These data can be interpreted as indicating a need for early intervention with radical cystectomy since a large majority of patients (79%-92%) treated with valrubicin are unresponsive to this treatment.

The FDA reviewer's final recommendations will be made after input from the Oncology Drugs Advisory Committee.

**CONCLUSION:**

The application has not provided convincing additional evidence that a special population of patients exists that would necessitate a change from the original decision to "not approve" the use of Valrubicin in patients with BCG refractory CIS of the bladder. Advanced age and comorbid medical conditions have not been adequately demonstrated to constitute a special population for whom approval is justified. An expansion of clinical criteria to include patients who recur with Ta G1/G2 disease has not altered the very low response rate of 8%-14% with this therapy. The studies conducted and the recent additional analyses, failed to establish evidence of sufficient clinical benefit to justify the potential risk of delaying cystectomy and potentially increasing the number of future deaths from bladder cancer. The number of deaths from metastatic bladder cancer in 46 non cystectomized patients in this study has steadily risen from 1 at the time of NDA submission in December 1997 to 4 at the time of ODAC presentation on June 1st 1998 and to 5 at the time of submission of the latest amendment on July 30 1998. On the contrary, there have been no bladder cancer related deaths in 44 cystectomized patients.

It is the view of this reviewer that this drug is still not approvable for any population of patients as represented through the study and the resubmitted application.

/S/

OLUWOLE O. ODUJINRIN MD. MPH. FACP

MEDICAL OFFICER

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# CHAPTER 29

# Management of Bladder Cancer in the Elderly

Eila Skinner, Derek Raghavan, Susan Kim, and Donald G. Skinner

## INTRODUCTION

Bladder cancer is predominantly a disease of aged populations in Western society, with most patients being aged 60 years or greater. In the community, the median age of presentation is 65 to 70 years of age, and in clinical trials, the median age of registered patients is in the range of 60 to 65 years.[1–3] In this context, the management of this cancer is governed particularly by the constraints imposed by the pathophysiology of the elderly, especially because the genesis of bladder cancer is heavily associated with cigarette smoking and industrial exposure, both of which cause significant intercurrent medical disorders in this population.[4]

The traditional view has been that treatment by radiation, surgery, or chemotherapy must necessarily be compromised in the elderly patient with bladder cancer. However, increasing experience in the management of these patients has shown this philosophy to be incorrect in most cases, especially in the context of the growing awareness of physical fitness among and improvements in medical care for the elderly.[4]

## PATHOPHYSIOLOGY OF AGING AND OF CANCER IN THE AGED

A detailed discussion of the pathophysiology of aging is beyond the scope of this chapter, and has been reviewed elsewhere.[4,5] Nevertheless, a brief overview is necessary to set the discussion regarding management of bladder cancer in the elderly into a context.

Age-related changes in the physiology of patients over the age of 70 may alter their tolerance to cancer and to the requirements of relevant treatment programs. There is a progressive reduction of physiologic reserves, with a general decline in the ability of the aging body to respond to physiological and pharmacological stresses.[6]

Specific age-related changes occur in different bodily functions. For example, cardiac output decreases by approximately 1% each year from the mid-twenties, with a consequent reduction in perfusion of the liver, kidneys, lungs, and gastrointestinal tract.[7] In patients with bladder cancer, a smoking-related disorder, cardiovascular function can be further impaired.[1] Pulmonary function is also affected by aging. There is a reduction in pulmonary compliance, as well as alveolar septal loss and a reduction in pulmonary diffusing capacity;[8] these changes will be exacerbated in patients with a history of smoking.

Age-related changes in renal pathophysiology include a reduction in weight, number of functioning nephrons, cortical volume, renal blood flow, and glomerular filtration rate.[9,10] Of particular importance when defining drug dosage, creatinine clearance may be an unreliable marker of renal function in the elderly patient; because there is less lean muscle mass, there is a concomitant reduction in creatinine clearance. Furthermore, patients with chronic analgesic nephropathy, usually predicated on excess ingestion of phenacetin, have an increased risk of urothelial malignancy[11]; such patients certainly comprise a subset of patients treated in clinical trials of bladder cancer management.[1]

Neurologic function also alters with aging, primarily due to a loss of functioning neuronal tissue. Changes in cognitive and behavioral function have been demonstrated in the central nervous system, accompanied by reductions in peripheral nerve function. These can be compounded by changes in cardiorespiratory function as noted above, as well as by intercurrent disorders, such as diabetes, alcoholism, and a range of iatrogenic situations.

In the gastrointestinal tract, changes in function with advancing age include: impaired peristalsis, slowed gastric emptying,[12] reduction in hepatic blood flow and liver mass, with unpredictable changes in hepatic function.[10] Gastrointestinal changes are frequently compounded by the ingestion of antacids, analgesics, laxatives, or by the reduction in cardiac output associated with aging. Similarly, bone marrow involutes progressively with increasing age and there is an apparent reduction in stem cell function.[13] In addition, a reduction in peripheral lymphocyte count, which may contribute to changes in immune function, has also been recorded with aging.[14] A wide range of other changes in the pathophysiology of the healthy body occur with aging,[4,5] and these may be compounded in the elderly patient with intercurrent diseases.

These issues must be taken into consideration when planning treatment for the patient with bladder cancer, whether the program will involve surgery, radiation, chemotherapy, or combinations of each of these. Although the otherwise healthy elderly

patient may tolerate active treatment programs without undue difficulty, consideration must be given to the possibility of reduced tolerance to stress or to the alterations in drug metabolism outlined above.

The other relevant issue is whether bladder cancer behaves differently in elderly populations. For example, it has been reported that bladder cancer is more advanced at presentation among the elderly in large epidemiologic series.[15,16] Similarly, in some surgical series, bladder cancer is more advanced at first presentation among elderly patients,[17,18] although this may simply reflect delayed presentation due to social factors (poverty, fear, delayed diagnosis). Nevertheless, Blandy and colleagues[17] did report a 12% 5-year survival rate among patients aged 75 to 91 years, compared to 57% for patients younger than 55 years. The reduced apparent cure rates in elderly patients reported in surgical series,[17,18] compared to younger cohorts, may reflect case selection, choice or timing of active management, or a range of other factors. By contrast, at the University of Southern California (USC), where an aggressive management approach has applied in recent years, no difference in 5-year survival was noted in a series of 108 patients, aged 70 years or older, compared with 373 younger patients (52% versus 55%) (Skinner and Skinner, unpublished data, 1994). However, this contrasts somewhat with the initial reported experience, in which patients aged 65 to 69 years had a 3-year disease-free survival of 58%, compared with 39% for patients older than 75 years.[19]

Holmes[16] has reported reduced differentiation of bladder cancer with increasing age, implying increased tumor aggressiveness. In autopsy series, the converse has been reported, with an apparent reduction in metastatic rate among the elderly.[20] If survival is used as the primary index of tumor aggression, outcome can be influenced by many factors, including patient selection, pattern of intercurrent disease, accuracy of death certificate data, and the biases contributing to selection of therapy. The Surveillance, Epidemiology and End Results (SEER) data show a decline in the observed 5-year survival rate for all tumors and stages with increasing age, but the situation changes if deaths from intercurrent disease are excluded.[21]

## SURGICAL CONSIDERATIONS

The urologist is involved in the diagnostic evaluation and surgical treatment of elderly patients with bladder cancer. The diagnostic techniques used in the office to determine the cause of hematuria or voiding complaints, including intravenous urography, ultrasound, and cystoscopy, are all easily performed on even the most debilitated and aged patient. After a bladder tumor is diagnosed, the management of the very elderly patient is more of a challenge.

Transurethral resection (TUR) is usually required to establish the histologic and staging criteria necessary for making further treatment decisions. A complete TUR is also the only treatment necessary for solitary, low-grade, superficial lesions (grade 1 or 2, stage Ta). TUR can be safely performed under spinal or epidural anesthesia, and apart from the general medical considerations for this type of anesthesia, no increase in surgical complications should be encountered in older patients. In fact, most simple elective procedures can be performed safely in elderly patients, provided that care is taken to manage their specific physiological problems.[22,23]

**TABLE 29-1.** *Indications for radical cystectomy*

1. Muscle invasive transitional cell carcinoma (TCC) of any grade
2. High grade TCC or carcinoma in situ refractory to intravesical therapy
3. Squamous cell or adenocarcinoma of the bladder
4. Low grade superficial TCC not controlled by transurethral resection and intravesical pharmacotherapy (rare)

Similarly, intravesical therapies (see Chap. 26), including bacillus Calmette-Guerin vaccine (BCG), thiotepa, mitomycin C, and doxorubicin, are all quite well tolerated in the elderly patient without specific age-related problems. The indications for use of intravesical therapies are identical for older and younger patients.

The management of high-grade, invasive cancer in elderly patients is much more difficult. When left untreated or undertreated, the tumor rapidly progresses, and death, from metastatic disease, occurs within 2 to 3 years. Few patients with metastatic bladder cancer die of intercurrent illness rather than the cancer itself. Furthermore, there may also be considerable morbidity from the primary tumor itself if the bladder is left in situ, including hemorrhage, pain, and urinary tract obstruction. Because of these factors, elderly patients with localized disease who are thought to have a 1 to 2 year life expectancy are best treated with an aggressive surgical approach, provided that anesthesiologic and medical considerations permit such an approach.[19,24]

The indications for radical cystectomy are listed in Table 29-1. Most patients undergo cystectomy for muscle-invasive, high-grade transitional cell carcinoma (TCC) or refractory carcinoma in situ (CIS). The surgical technique has been described elsewhere.[25] Meticulous lymph node dissection adds little to the surgery in the way of morbidity, but does contribute significant staging information and is curative for up to 20% of patients with microscopic nodal disease.[26] At USC, a complete bilateral pelvic lymph node dissection is routinely performed at the time of cystectomy.

Although partial cystectomy has been portrayed as an attractive alternative in a frail patient, the results are often disappointing. Tumor spillage is inevitable during partial cystectomy, and thus pelvic recurrence is a significant concern. More importantly, partial cystectomy does not address the multifocal nature of bladder cancer, and thus 40% to 70% of patients treated in this fashion have recurrences in the retained bladder segment.[27] At USC, partial cystectomy is reserved for the rare patient with squamous cell carcinoma or adenocarcinoma of the dome, or a tumor in an isolated bladder diverticulum.

The key to successful major surgery in the elderly patient is a team approach, including anesthesiologists and intensive care specialists with experience in the management of the elderly surgical patient. A short but effective 1-day antibiotic and mechanical bowel preparation with intravenous hydration the night before surgery minimizes potential electrolyte imbalance. Prophylactic use of digitalis is applied routinely at USC in all patients over 65 years of age. The fluid shifts attendant with major pelvic surgery are not well-tolerated by elderly patients with impaired renal and cardiac function, and invasive cardiopulmonary monitoring is very helpful during the perioperative period.

Controlled hypotensive anesthesia minimizes blood loss but must be applied very carefully in the patient with significant coronary or cerebrovascular disease. Prophylaxis against venous thrombosis is crucial because pulmonary embolism is one of the most common causes of operative mortality with this operation. At USC, postoperative anticoagulation with warfarin sulfate is used routinely until the patient is fully ambulatory. Of great importance, nutritional status must be monitored carefully, and parenteral or enteral supplementation is used as needed to avoid a prolonged catabolic state.

Surgical mortality from radical cystectomy in elderly patients ranges from 3% to 6% in modern series, compared to 1% to 3% in younger patients—a modest increase considering the range of intercurrent medical disorders present in most elderly patients. Reported complication rates are also somewhat higher in older patients, ranging from 30% to 50%.[19,24,28,29]

Preoperative medical problems do not always predict postoperative complications. Although 26 patients in the early USC series had preexisting cardiac disease, only 8 of them had postoperative cardiopulmonary complications, most of which were minor arrhythmias.[19] A total of 141 patients aged 75 years or older have now been treated at USC by radical cystectomy or anterior exenteration. Sixty-nine of them were aged 80 years or older. The male to female ratio was 2:1, compared to approximately 5:1 for younger patients. The operative mortality rate was 3%, and the early complication rate 32%, with an average hospital stay of only 14 days.

Continent urinary diversion has become a widely accepted alternative to the ileal conduit in many parts of the world. However, a bias persists in many centers, where this option is offered only to younger patients. At USC, continent diversion has been performed in 84 patients aged 75 years and older, including 41 cutaneous Kock pouches, 41 Kock neobladders, and two ileoanal reservoirs. There was no difference in the early complication rate for these patients compared with those who had ileal conduits. This finding has been confirmed by several other groups performing continent diversion who have not routinely excluded older patients.[30,31]

The orthotopic neobladder is also a viable alternative for older men, and it is being assessed for women as well. AT USC, Kock pouch neobladders have been constructed in 41 males with bladder cancer, aged 75 years or older, including 8 older than 80 years of age. Continence seems to be achieved more slowly in the elderly, but most attain satisfactory results regardless of age.

For patients severely debilitated by intercurrent medical diseases, such as cardiac dysfunction, chronic airflow limitation or cirrhosis, a high operative mortality may be unavoidable. In these patients, treatment with radiotherapy or combined chemotherapy and irradiation may offer a useful alternative. However, patients should not be discouraged from surgical consideration based purely on age criteria. For example, many patients referred to the Department of Urologic Surgery at USC for consideration of salvage cystectomy for pelvic relapse, 1 to 2 years after radiotherapy, had been advised against surgery at their initial presentation because they were "too old."

## RADIOTHERAPY FOR BLADDER CANCER IN THE ELDERLY

There has been considerable debate regarding the optimal treatment of invasive bladder cancer, and whether radical radiotherapy yields equivalent outcomes to radical surgery.[32] In the United States, there has been a clear bias in the selection of patients for radiotherapy, with the emphasis being on its use in patients of more advanced age, especially those deemed medically unsuitable for radical cystectomy. By contrast, in Great Britain and in some regions in Europe, more equivalent age distributions have been reported, reflecting a greater predelection for the use of radiotherapy as a standard treatment for bladder cancer.

Radiation therapy has been applied to the treatment of bladder cancer in several ways (see Chap. 27), including external beam therapy alone in a definitive or palliative setting, as preoperative or postoperative adjuvant therapy, sequentially or concurrently with chemotherapy, as interstitial brachytherapy, and as intraoperative radiation therapy. Initial complete response rates with radiotherapy alone have ranged from 40% to 50%. However, 30% to 50% of patients subsequently relapse locally, yielding an ultimate local control rate of only 25% to 30%.[33–36]

The application of radiotherapy to the treatment of bladder cancer in elderly patients requires meticulous preparation.[37] A balance must be achieved between the optimal dosage required for tumor control and the potential for iatrogenic morbidity. Several factors must be considered: the altered potential for normal tissue toxicity; the difficulty of treating an elderly patient experiencing borderline dementia or confusion in the isolation of a radiation treatment room; and the potential physical difficulties for the unfit patient undergoing planning and treatment, including the need for the patient to assume a prone position for treatment (particularly difficult for patients with severe airways disease or arthritis).

Once a patient is deemed eligible for radiation therapy, a treatment technique must be defined; many are feasible for elderly patients. Initially, simulation or treatment planning is performed to define the treatment volume. The patient is placed in either a supine or prone position, depending upon the preferred treatment technique. A 4-field box, 3-field technique with wedges, rotational arcs or even parallel opposed fields with high energy x-rays are acceptable, depending upon dose homogeneity. A Foley catheter is inserted and 30 mL of contrast medium and 10 mL of air are placed into the bladder. A rectal tube, with or without barium, is inserted to localize the rectum. At Roswell Park Cancer Institute, locoregional lymphatics, including the external and internal iliac chains, are included in the initial target volume, with a superior border at the L5-S1 region or the sacroiliac joints and the lateral border 1.5 cm beyond the pelvic brim. The inferior margin is placed at the ischial tuberosity if the bladder neck or prostatic urethra are involved, but otherwise at the obturator foramen. At 45 Gy to 50 Gy, the treatment fields are reduced to include only the tumor encompassed by a 1.5–2.0 cm margin of normal tissue. The large pelvic fields are treated while the patient has an empty bladder to ensure that the entire bladder is included, but with the boost volume, the treatment may be delivered with the bladder full to ensure that only the tumor volume with margin receives the additional treatment. The total recommended dose ranges from 64.8 Gy to 68.4 Gy, with fraction sizes of 1.8 Gy to 2.0 Gy. For elderly patients unable to tolerate a large treatment volume, it may be necessary to restrict treatment to the bladder only with a small margin, the justification being that isolated regional failure is an uncommon occurrence. If radical doses of radiotherapy are contraindicated, a typical palliative schedule

can be employed, for example, 30 Gy in 10 fractions, using anterior-posterior/posterior-anterior fields. If the patient cannot tolerate 2 weeks of consecutive daily radiation treatments, single-fraction high-dose treatments (6.0 Gy to 10 Gy) delivered each month for 3 to 4 doses may be another option.

Several factors which may contraindicate definitive radiation therapy in any patient should also be considered in the elderly population. For example, patients who already have compromised bladder function due to contracture probably will not benefit, and will often deteriorate, after radiotherapy. Palliative irradiation may also be more appropriate for patients with T4 tumors, tumor size greater than 7 cm, and tumors with significant ulceration, because definitive treatment in these settings is associated with poor survival and greater morbidity.[34] In addition, patients with inflammatory bowel disease and those who have previously undergone extensive pelvic or bowel surgery may have prohibitive side effects when high radiation doses are administered.

Even in the otherwise healthy elderly patient, morbidity rates from radiotherapy can be significant. Acute side effects include diarrhea and cystitis; these can be controlled with conservative measures, such as the use of antispasmodics and antidiarrheals, as well as a change to a low-residue diet. Some patients will complain of nausea, and others will suffer nonspecific problems, such as severe fatigue or lethargy, and occasionally anorexia.

Long-term side effects such as bladder contraction, hemorrhagic cystitis, bowel obstruction, or gastrointestinal hemorrhage, have been recorded in as many as 14% of cases,[34] although the rate has been lower in series with lower fraction sizes, and more sophisticated treatment planning and more stringent case selection.[38–40] Similarly, treatment-related mortality, as high as 1.2%,[34] may be reduced by decreasing the daily fraction size, improvements in treatment planning, and by case selection.

Consideration of the use of radiation therapy in the elderly is complicated somewhat by the lack of consensus regarding the prognostic implication of advanced age on the outcome of radiotherapy for bladder cancer.[33–36,41] For example, in the Edinburgh series, 917 patients with T1 to T4 TCC were treated definitively with radiation alone; 44 were aged 79 years or older. A dose of 55 Gy to 57.5 Gy was delivered in 20 fractions, using a 10 cm by 10 cm field size over 4 weeks.[34] A complete response was achieved in 45% of patients, but approximately 50% relapsed locally, and only 30% were alive at 5 years. When analyzed by age, the survival rate for patients younger than 65 years was about 50%, compared to less than 30% for those aged 70 to 79 years, and only 11.6% for patients older than 79 years. Even when the series was corrected for intercurrent disease, the most elderly patients suffered the poorest outcomes. Similarly, at the London Hospital, where 704 patients with T1 to T4 tumors were treated with radical radiotherapy, only 12% of patients aged 75 years or older were alive at 5 years.[17] However, in this series, patients only received doses less than 50 Gy.

Because age has not been an independent prognostic factor in other studies,[35,42] it may be that dose modifications might have been the basis of impaired outcomes in the series from Edinburgh and London, especially since a dose of less than 55 Gy has been reported as an important adverse prognostic determinant.[40] Other prognostic determinants for response to irradiation, such as T stage, grade, size, presence of ureteral obstruction, anemia, and prior transurethral resection, have been identified,[35,36,42,43] but do not consistently appear to be associated with advanced age per se.

## CHEMOTHERAPY

One important application of cytotoxic chemotherapy is in the context of intravesical administration for treatment of superficial bladder cancer, or as prophylaxis after transurethral resection (see Chap. 26). However, there are no major age-related issues in the latter context, apart from the fact that the elderly male patient may have an enlarged prostate, making repeated urinary catherization more difficult, or may have greater problems with the retention of intravesical solutions for the requisite period of 1 to 3 hours.

There are two major situations in which systemic cytotoxic chemotherapy is employed for elderly patients with bladder cancer, and in both instances, considerable data are available regarding the age-related issues that arise: (1) the initial management of invasive disease as part of a program of multimodality treatment (neo-adjuvant, concurrent, or classical adjuvant chemotherapy); and (2) the treatment of metastatic or locoregionally relapsed bladder cancer.

Many of the physiologic and pathologic changes associated with the aging process may alter the pharmacology of cytotoxic agents, influencing such parameters as gastrointestinal absorption, renal or hepatic excretion, drug distribution, and dose-response relationships.[4] It is important to note that the elderly have a greater propensity to receive multiple medications,[44] are at risk for poor compliance with complicated schedules of oral medication, and have increased potential for adverse drug interactions.

There is considerable controversy about whether the toxicity of chemotherapy is increased in the elderly. It appears that this varies both with the disease being treated and the nature of the treatment. Although early data suggested that methotrexate and bleomycin cause greater side effects in aged patients,[45,46] studies from the Eastern Cooperative Oncology Group have shown that toxicity in the elderly is a function of the agent and the dose employed, rather than being attributable specifically to age.[47] These studies confirmed the age-related toxicity of methotrexate, but did not show similar effects for doxorubicin, cyclophosphamide, the vinca alkaloids or mitomycin. Furthermore, cisplatin toxicity is not age-related.[48,49]

Several metabolic functions may be influenced by the underlying disease and its etiology. In the case of bladder cancer, with a strong smoking-related etiology, the cardiac toxicity of doxorubicin and the pulmonary side effects of mitomycin may be unpredictable; similarly, with the potential for renal dysfunction associated with bladder cancer, the toxicity of methotrexate or cisplatin can be severe. Attention to dosage, the use of folinic acid rescue, and meticulous use of hydration schedules are key.

There has been disagreement with regard to dose reductions in elderly patients, with the consequent reduction in dose intensity. Although data have been published for a range of malignancies, as reviewed previously,[4,23] little information is available regarding the issue of dose modification in the treatment of bladder cancer in elderly populations. Scher and coworkers[50] analyzed retrospectively their experience with dosing of the MVAC regimen in the full Memorial Sloan-Kettering Cancer

Institute series of 132 cases, and compared outcomes for patients treated with full-dose therapy, including all day 15 and day 22 booster injections, versus the situation when boosters were omitted. In this study, there was no evidence of impaired survival in the group receiving dose reductions, although the numbers of cases in each group were relatively small, and a small survival difference could have been neglected. This suggests that there may be little benefit in emphasizing dose intensity, at least in the more aged subgroup of such patients.

## Invasive Bladder Cancer

The role of systemic chemotherapy for invasive, clinically nonmetastatic bladder cancer is discussed in Chapter 28. Although most of the published data with respect to the integration of systemic cytotoxics into combined modality strategies for invasive bladder cancer have reported patients of all age groups, a few published reports have addressed specifically the use of chemotherapy for the management of invasive bladder cancer in elderly populations. For example, as part of a broader study of patients treated with single-agent cisplatin (100 mg/m$^2$ IV) as neoadjuvant therapy before definitive radiotherapy or cystectomy, we assessed the impact of this strategy in the treatment of patients aged 70 to 79 years.[49] Although they had a broad range of smoking-related disorders, characteristic of elderly patients with bladder cancer, subjectively and objectively, these patients tolerated the treatment program remarkably well, and 33% survived 3 years or longer (Table 29-2). These observations were tested further in a randomized trial in Great Britain and Australia, comparing cisplatin plus radiotherapy versus radiotherapy alone.[51] Although no significant survival benefit was shown from the use of neoadjuvant cisplatin, it was clear that age was not an independent adverse prognostic determinant. Similarly, Shearer and colleagues[52] showed that single-agent methotrexate did not confer an improved survival when used as neoadjuvant therapy, but also confirmed that age was not an independent prognosticator of survival. However, they did demonstrate that advance age was associated with greater methotrexate-related toxicity.

Combination chemotherapy has also been used without excessive toxicity in the treatment of elderly patients with invasive bladder cancer, although the specific age-related toxicities have not always been dissected out for the older patients.[53,54] Sella

**TABLE 29-2.** *Neoadjuvant cisplatin for septuagenarians with locally advanced bladder cancer*

| Sex | Age | ECOG performance status | Other disorders | Stage | Grade | Acute toxicity | Objective response (CR or PR) | Survival (Months) |
|---|---|---|---|---|---|---|---|---|
| F | 71 | 0 | Uterine fibroids | T3 | III | NV grade 2 | Yes | 35 |
| M | 76 | 0 | — | T4a | III | NV grade 2 | Yes | 63+ |
| F | 72 | 1 | Hypertension, cataracts | T3 | III | NV grade 3, renal grade 2, high tone deafness, dehydration | No | 6 |
| M | 70 | 0 | NIDDM, AAA, old TB | T3 | III | NV grade 2, diarrhea grade 2 | Yes | 50+ |
| M | 78 | 0 | — | T3 | III | NV grade 2, renal grade 2 | Yes | 8 |
| M | 70 | 0 | Hypertension, inguinal hernias | T3 | III | NV grade 2, renal grade 2 | Yes | 13 |
| M | 79 | 0 | Atrial-fibrillation, CCF | T4a | III | NV grade 2, confusion, incontinence | Yes | 13 |
| M | 71 | 0 | — | T2+ | III | NV grade 2, diarrhea | Yes | 36 |
| M | 70 | 0 | COAD, right inguinal hernia, essential tremor | T2 | III | NV, neutropenia grade 1 | Yes | 48+ |
| M | 71 | 0–1 | Peptic ulcer disease, renal calculi, thromboasthenia | T2 | III | NV grade 3, neutropenia grade 2, dehydration | Yes | 22 |
| M | 75 | 0 | Glaucoma | T2+ | III | NV grade 2 | Yes | 36+ |
| M | 70 | 1 | Hypertension, COAD, renal calculi | T3 | III | NV grade 3 | Yes | 17 |
| F | 76 | 0 | Hypertension, atrial fibrillation | T2+ | II | NV grade 3, atrial fibrillation, femoral embolus | Yes | 14 |
| M | 77 | 0 | Esophageal stricture, reflux, renal calculi, ischemic heart disease | T4a | III | Sedation, neutropenia grade 1 | Yes | 14 |
| F | 70 | 0 | Varicose veins | T3 | III | NV grade 2–3 | Yes | 29 |

AAA, abdominal aortic aneurysm; CCF, congestive cardiac failure; COAD, chronic obstructive airways disease; ECOG, Eastern Cooperative Oncology Group; NIDDM, non—insulin-dependent diabetes mellitus; NV, nausea and vomiting; TB, tuberculosis; T2+, at least stage 2.

From Raghavan D. Management of advanced bladder cancer in the elderly. Urol Clin North Amer 1992;19:797.

TABLE 29-3. *Age as prognostic factor in patients treated with chemotherapy for advanced bladder cancer*

| Age (years) | | | | | |
|---|---|---|---|---|---|
| Median | Range | No. of patients | Regimen | Age as adverse prognostic factor | Reference |
| 62 | 23–77 | 132 | M-VAC | No | 57 |
| 66 | 30–79 | 126 | M-VAC | No | 3 |
| 64 | 35–82 | 120 | C | No | 3 |
| 65 | 35–75 | 55 | C | ? | 2 |
| 63 | 40–74 | 53 | MC | ? | 2 |
| 78 | 76–84 | 36 | M-VAC, CMV, CyAC | No? | 55 |
| 71 | 70–79 | 15 | C & RT | No | 49 |

A, doxorubicin (Adriamycin); C, cisplatin; Cy, cyclophosphamide; M, methotrexate; RT, radiotherapy; V, vinblastine.

From Raghavan D. Management of advanced bladder cancer in the elderly. Urol Clin North Amer 1992;19:797.

and coworkers[55] treated 18 patients with high-grade, locally extensive bladder cancer, aged 75 years or older, using cisplatin-based combination therapy after control of the primary tumor. These patients were carefully selected on the basis of good performance status and renal function. Nevertheless, more than 20% withdrew from therapy because of toxicity, and 33% had significant infectious complications. The median survival of this group, despite the aggressive therapy, was only 23 months, not greatly different from the figures obtained from series of patients treated with single agent cisplatin or methotrexate as neoadjuvant therapy.[49,52] In addition, it should not be forgotten that randomized trials have not yet proven the role of neoadjuvant or classical adjuvant chemotherapy in this context (see Chap. 27). Of interest, a study of the role of adjuvant chemotherapy with cisplatin, doxorubicin and cyclophosphamide at the University of Southern California, which has caused some controversy in interpretation, demonstrated that patients aged more than 65 years constituted a subgroup with a better outcome, irrespective of the use of chemotherapy.[56] This observation will bear further study.

### Recurrent and Metastatic Disease

The management of recurrent invasive bladder cancer or metastatic disease constitutes a complex problem, irrespective of the age of the patient, and median survival times are usually less than 3 years, irrespective of the age of the patient.[32] Radiotherapy or salvage cystectomy will occasionally yield long-term survivors, but the relative lack of success in the treatment of younger patients has led to significant nihilism in the management of older patients. In addition, most trials of chemotherapy for metastatic or recurrent disease have yielded median survival times of only 12 to 18 months, with 5-year survival rates of only 10% to 20%.[32]

Few studies have specifically addressed the role of chemotherapy for aged patients with metastatic bladder cancer (Table 29-3). In a retrospective study of prognostic factors among the patients treated with the combination of methotrexate, vinblastine, doxorobucin, and cisplatin (MVAC) for metastatic bladder cancer at Memorial Sloan-Kettering Cancer Center, Geller and colleagues[57] showed improved survival among patient aged 60 years or older. Using the Cox proportional hazards model, normal alkaline phosphatase, high Karnofsky performance status, and age of 60 years or more were shown to predict improved survival. However, the possibility that selection factors could have influenced outcome was not excluded.

Similarly, in an international randomized trial carried out by the Eastern Cooperative Oncology Group, Southwest Oncology Group, National Cancer Institute of Canada and Australian Bladder Cancer Study Group, we showed equivalent survival figures among the elderly patients and younger cohorts.[3] In this study, the first to demonstrate a survival benefit from MVAC chemotherapy compared to single agents, nearly 45% of the 269 patients were 64 years or older.[3]

Sella and coworkers[55] reported 18 patients, aged 76 years or older, with metastatic bladder cancer, who received a range of cisplatin-containing combination regimens, including MVAC. Seven patients (39%) had objective responses, including two with complete remissions. However, the median survival in this study was only 10 months, the treatment was clearly toxic, and dose intensity was not predictive of outcome. In this context, one could question whether such intensive treatment was appropriate for metastatic bladder cancer in this elderly population group.

## SUMMARY

Patients in their eighth decade are becoming an increasingly important group numerically in the practice of uro-oncology, and it will be necessary to develop more sophisticated and flexible approaches for their management. Provided that care is taken to plan for their altered physiologic requirements, it is clear that comparable (or better) outcomes can be anticipated from well-designed treatment programs that involve surgery, radiation or chemotherapy, applied as single modalities or in combination. Given the potential for successful outcomes of treatment, we must place greater emphasis on educating the elderly about the symptoms of bladder cancer, encouraging them to present as early as possible, thus facilitating the best possible results of treatment. Advanced age alone should not preclude the provision of active and effective strategies of treatment.

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