

Clinical Update

Development of Systemic and Topical Drugs to Treat Non-muscle Invasive Bladder Cancer

Jonathan Jarow^a, V. Ellen Maher^{b,*}, Shenghui Tang^c, Amna Ibrahim^b, Geoffrey Kim^b,
Rajeshwari Sridhara^c and Richard Pazdur^b

^aOffice of Medical Policy, Center for Drug Evaluation and Research, FDA, MD, USA

^bOffice of Hematology and Oncology Products, Center for Drug Evaluation and Research, FDA, MD, USA

^cOffice of Biostatistics, Center for Drug Evaluation and Research, FDA, MD, USA

Abstract. There are few approved drugs available for the treatment of patients with non-muscle invasive bladder cancer (NMIBC) and none have been approved in the twenty-first century. Four drugs; thiotepa in 1959, BCG Tice in 1989, BCG Connaught in 1990, and valrubicin in 1998, have been approved for the treatment of NMIBC. In addition to these four agents, mitomycin is commonly used off-label as an intravesical treatment for NMIBC. New drugs are needed for the management of NMIBC. This article outlines important aspects of the design and conduct of clinical trials to develop new therapies for these patients and to obtain marketing approval. It includes a discussion of the patient population, BCG-unresponsive disease, and the appropriate endpoints for drug approval. It is hoped that this article will spur drug development in NMIBC within the Center for Drug Evaluation and Research at the Food and Drug Administration.

Keywords: Non-muscle invasive bladder cancer, drug development, clinical trial design

INTRODUCTION

Non-muscle invasive bladder cancer (NMIBC) is a localized disease of the bladder urothelium generally managed with surgical resection and/or intravesical therapies. The main goals of these therapies are to prevent recurrence and progression of the patient's bladder cancer. More effective drugs and drugs that are active in refractory patients are needed in NMIBC. This article outlines important aspects of the design and conduct of the clinical trials necessary to obtain marketing approval.

PATIENT POPULATION

Non-muscle invasive bladder cancer includes the following clinical stages of disease:

- Ta: Non-invasive papillary cancer;
- T1: Tumor invades the subepithelial connective tissue; and
- Tis: Carcinoma *in situ* [1].

Among patients with bladder cancer, approximately 45% present with Ta, 24% with T1, and 10% with Tis. The remainder of the patients present with >T2 disease (muscle-invasive bladder cancer) [2]. To fully establish the tumor stage, it is important that the biopsy specimen contain muscle tissue. To this end, patients who have undergone resection of a T1 lesion should undergo biopsy of the base of the lesion before study entry to confirm the absence of muscle-invasive

*Correspondence to: V. Ellen Maher, US Food and Drug Administration, WO22-2352, 10903 New Hampshire Ave., Silver Spring, 20993-0002 MD, USA. Tel.: +1 301 796 5017; Fax: +1 301 796 9845; E-mail: virginia.maher@fda.hhs.gov.

disease. Further, patients with high-grade T1 disease or non-papillary lesions should undergo imaging by CT scan or MRI. To fully determine the patient's risk of recurrence or progression, both tumor stage and grade should be assessed. The 2004 World Health Organization/International Society for Urological Pathology system is the preferred system for tumor grading [3]. This system categorizes tumors as either low or high grade. Central review of pathology specimens, to evaluate both stage and grade, at study entry and on subsequent biopsy is encouraged.

Tumor stage and grade can be used to categorize the risk of recurrence and progression of the patient's tumor. The following risk categories are typically used [4–6].

- Low-risk tumors include small volume, low grade Ta lesions with no evidence of Tis.
- Intermediate-risk tumors are variably described and include those that cannot be categorized as either low- or high-risk such as large volume or recurrent low-grade Ta disease.
- High-risk tumors include T1 lesions of any grade, high grade Ta disease, and Tis.

Most patients with intermediate- and high-risk NMIBC are treated with an induction course (6 weekly instillations) and maintenance (3 weekly instillations at 3 and 6 months and every 6 months thereafter) of bacillus Calmette-Guérin (BCG) [7]. While the majority of patients are successfully treated with induction and maintenance BCG, some patients are unresponsive or recur after a short time. The Society for Urologic Oncology has recently agreed upon the following definition for a population that has BCG-unresponsive disease and is extremely unlikely to benefit from further BCG therapy [8]. Radical cystectomy is the most effective treatment alternative for these patients.

- Patients with persistent high grade disease or recurrence within six months of receiving at least 2 courses of intravesical BCG (at least 5 of 6 induction and at least 2 of 3 maintenance doses of BCG)
- Patients with T1 high grade disease at the first evaluation following induction BCG (at least five of six doses).

In clinical trials, investigators should carefully document prior BCG dosing and response. It is important to distinguish BCG-unresponsive disease from either inadequate therapy or BCG-intolerance because of the significant difference in prognosis.

TRIAL DESIGNS

Options for early phase clinical development include the examination of the treatment activity of the investigational agent in patients with marker lesions or in patients undergoing cystectomy. Marker lesions are small (<3 cm) areas of low grade papillary carcinoma that are biopsied and left in place to subsequently assess anti-tumor activity. Following administration of study drug, these lesions are subsequently examined cystoscopically for response to the experimental drug and residual disease is resected. The number of patients involved in these “proof of concept” studies should be limited to as few as necessary to demonstrate the anticipated magnitude of activity and they should be followed closely. Alternatively, the study drug may be administered to patients with residual disease who are awaiting cystectomy. This approach is particularly advantageous for patients with Tis, in whom marker lesions are not reliably assessed. In addition, this approach allows examination of activity over the entire bladder through pathological assessment of the surgical specimen. Drawbacks to this approach include the limited time window available for observation of activity after the last dose of study drug since surgery should not be delayed and patients should not forego neoadjuvant chemotherapy to permit study of a new drug.

In late phase clinical development, priority should be given to the use of randomized controlled superiority trials rather than single-arm designs. Single-arm trials may be considered for situations in which it is unethical to randomize patients to a placebo control or in which an appropriate active control does not exist. A placebo control may be considered in patients without a significant risk of progression such as patients with low-risk and possibly intermediate-risk disease. For intermediate- and high-risk disease, a randomized superiority trial against an appropriate active control or a randomized trial in which the experimental therapy is added to the standard of care (e.g., BCG ± experimental therapy) is recommended. For example, patients with persistent/recurrent disease after a single induction course of BCG could be randomized to additional BCG vs. experimental therapy or to BCG ± experimental therapy. In patients with BCG-unresponsive disease, radical cystectomy should not be unduly delayed while awaiting a response to an experimental agent.

Single-arm trials may be considered when an appropriate control does not exist (e.g., patients with BCG-unresponsive disease). The statistical analysis plan should be pre-specified for all trials. For a single-arm

trial, the statistical plan should include a historical control based on the entry criteria and endpoints employed. For trials with a regulatory intent, it is advisable to discuss the trial design in advance with the appropriate review division of the FDA. The Agency realizes that historical controls may provide an imprecise estimate of contemporary patient outcome and recommends that the chosen historical controls be discussed with the Agency prior to trial initiation.

A critical factor in the design of any trial is the entry criteria. Patients with NMIBC have a varying risk of recurrence and progression even within the conventional risk strata. Thus, it is important that entry criteria are strictly defined in all trials and patients are stratified by their risk strata in randomized trials. For example, it is reasonable to include patients with Tis and papillary disease (T1, or high grade Ta) in the same trial, but to stratify to ensure equal distribution of patients with Tis, T1, or high grade Ta disease between arms.

The investigator performing the cystoscopy has an important impact on patient staging and outcome. Therefore, consideration should be given to stratification by investigative site or geographic location. Even with this stratification factor in place, it is important to ensure that all urologists participating in a trial are examining and documenting their examination of the bladder as pre-specified in the protocol. Consideration should be given to stratification by whether or not the urologist uses fluorescence-guided cystoscopy in the examination of the bladder.

ASSESSMENTS

Central review of pathological and radiological assessments should be considered for the primary endpoint of trials with regulatory intent. Nevertheless, real-time central pathological assessment is not always feasible and, therefore, immediate treatment decisions for patients with NMIBC are often based on local pathology. In this setting, the preferred option is to use the local pathology assessment in the analysis of the primary endpoint. Central pathological review of patient biopsy(ies) at study entry and biopsies performed as part of on-study assessments should be conducted to support a marketing application. This, ideally, should be done in all patients. In a large study, use of central review can be considered, at a minimum, in a representative/random sample to ascertain lack of bias in the local pathology assessments. The results of analyses based on the findings of the central pathology review should be consistent with the primary analysis based on local pathology.

In studies intended for marketing approval, patients should undergo cystoscopy and cytology every 3 months for the first two years. An alternative schedule may be considered for trials that include only patients with low-risk disease. Bladder biopsy/transurethral resection should be performed for abnormal cystoscopy (directed) or abnormal cytology (random). In addition, scheduled biopsies, including random biopsies in the absence of a visual lesion, should be considered at key time points (e.g., at 18 months if this is a secondary endpoint). Further, scheduled biopsies to assess complete response in patients with Tis should be performed six months after initiation of therapy. Mandatory biopsies at regular intervals are not required to determine the duration of complete response. If fluorescence-guided cystoscopy was used at baseline, fluorescence-guided cystoscopy should be used at each of the follow up assessments.

ENDPOINTS AND STATISTICAL PLAN

The study endpoint should be based on the type of disease at study entry. Since patients with Tis have objective evidence of disease at study entry, the rate and median duration of complete response can be used as the primary endpoint for either single-arm or randomized trials. Here, the lower bound of the 95% confidence interval around the response rate should be compared to a historical control rate. Given the uncertainty in the comparison to historical controls, the trial should be designed to demonstrate a clear (large) improvement over historical controls. Further, selection of the appropriate historical control is critical. One approach is to conduct a case-control study in which patients are matched to historical controls based on their disease characteristics and extent of prior therapy.

The preferred endpoint for a study of patients with pure papillary disease, since they do not have objective evidence of disease at study entry, is a time-to-event analysis of event-free survival (EFS) using Kaplan-Meier estimates. In this context, recurrence of disease, progression, or death is considered an event. The evaluation of EFS should be event driven and should be analyzed using survival analysis methodology in randomized clinical trials. Secondary endpoints may include EFS rate at specific time points (e.g., 12 or 18 months).

Particularly in the setting of BCG-unresponsive disease, single-arm and randomized trials may include a mixture of patients with Tis alone and patients with papillary disease with or without concomitant Tis. The

preferred primary endpoint when a mixed population is studied in a single-arm trial is the rate and median duration of complete response for the subgroup of patients with Tis at entry. Here, the EFS for the recurrence of papillary disease is descriptive and is considered supportive of the primary endpoint of response rate in the Tis subgroup. The preferred primary endpoint when a mixed population is studied in a randomized trial is EFS. In such a trial, patients with both papillary disease and Tis may fail to achieve a complete response, develop recurrent papillary disease, develop recurrent Tis (after a complete response), or die prior to these events. For EFS, patients with Tis alone or Tis and papillary disease who do not have a complete response would have their event at time zero. Patients with papillary disease alone may develop recurrent papillary disease, new onset Tis, or may die prior to these events.

An additional issue in the selection of the appropriate endpoint is the inclusion of low grade recurrences or upper tract disease in the primary analysis. While the development of upper tract disease will affect patient outcome, intravesicular therapy is unlikely to influence the development of disease in the upper tract. Therefore, occurrence of upper tract disease should not be included as an event in trials of intravesicular therapy(ies). Since systemic therapies may impact disease in both the upper tract and the bladder, upper tract disease should be included as an event in studies of systemic agents. Likewise, in some situations, it may be reasonable to exclude low-risk disease from the primary endpoint. For example, a trial involving patients with BCG-unresponsive disease could include only the recurrence/persistence of high-risk disease in the primary endpoint. Here, a low-risk recurrence leads to transurethral resection while a high-risk recurrence leads to cystectomy, a much different clinical outcome. It is, therefore, reasonable to include only high-risk disease in the primary endpoint. If low-risk disease is not included in the primary endpoint, an analysis of all cancer recurrence/persistence will be an important secondary endpoint and the results of this analysis should be consistent with the analysis of the primary endpoint. Finally, the recurrence/persistence of high-risk disease, rather than a delay in cystectomy should be the primary endpoint in studies of patients with NMIBC. While a delay of cystectomy could be considered a direct patient benefit, variability due to both healthcare provider and patient preference makes a delay in cystectomy difficult to interpret. Therefore, the persistence/recurrence

of high-risk disease is the preferred primary endpoint.

The intravesicular therapies approved to date have had a favorable risk-benefit profile due to the relatively low toxicity of these products. The approval of a marketing application is based on a risk-benefit assessment. The key elements in the planning and conduct of these trials have been outlined above. Significantly greater efficacy would be expected for therapies (e.g., systemic therapies) that display greater toxicity. Sponsors of clinical trials using either intravesicular or systemic therapy are encouraged to meet with the FDA to discuss details of their trial designs.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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