THE UNIVERSITY OF ARIZONA
College of Medicine
Phoenix

Salvage Hyperthermic Gemcitabine and Docetaxel Combination Chemotherapy After BCG Failure in Non-Muscle Invasive Bladder Cancer Patients

Mounica Y Rao [1], Paul Kang [1], Jamaka C Tarjkowski [2], Debra L Mobley [2], Donald L Lamm, MD [1,2]

[1] University of Arizona College of Medicine- Phoenix, [2] BCG Oncology

Abstract

While the treatment success rates of Bacillus Calmette-Guerin (BCG) in non-muscle invasive bladder cancer (NMIBC) are high, there are still patients who fail this therapy or are not good candidates for it. The purpose of this study is to analyze if combination Gemcitabine and Docetaxel chemotherapy (GEM/DOCE) is a successful salvage option in adults who have failed or cannot tolerate BCG therapy for NMIBC and are poor surgical candidates for a radical cystectomy (RC) or desire bladder preservation. In this retrospective study, 60 patients were included. Overall treatment success was 83% (50/60) at first surveillance, 69% at 1-year, and 55% at 2-years after induction of GEM/DOCE in the entire cohort, and 90% (53/51) at first surveillance, 74% at 1-year, and 56% at 2-years in the BCG-failure patients. These success rates are quite favorable and warrant further investigation in a prospective manner to further optimize this salvage protocol for patients who remain a challenge to treat.

Introduction

Current guidelines state that disease management of NMIBC should include intravesical BCG immunotherapy for intermediate and high-risk tumor patients. Up to 40% of individuals with NMIBC won't respond to intravesical BCG therapy and up to 75% of individuals will develop a new tumor within 5 years.

In cases of BCG failure, RC is the preferred option, however many patients prefer bladder preservation after considering the potential morbidity and mortality associated with RC, while others are not surgical candidates. In this situation, salvage intravesical treatments have become an important option for patients.

The purpose of this study is to answer the question, in adults who have failed BCG therapy for NMIBC, and are poor surgical candidates for RC or desire bladder preservation, is combination Gemcitabine and Docetaxel chemotherapy a successful salvage option? This study is a retrospective review of patients who have failed or could not tolerate BCG therapy for NMIBC and opted to receive concentrated, intravesical, hyperthermic combination Gemcitabine and Docetaxel chemotherapy at BCG Oncology.

Methods

Patients who failed BCG therapy for NMIBC and opted to receive combination GEM/DOCE chemotherapy between 2007-2017 at our institution were identified (*n = 60*) and retrospectively reviewed. **This study measured overall treatment success, defined as no bladder cancer recurrence, no progression to muscle invasion or metastasis, no cystectomy, and no death due to bladder cancer.** Time to recurrence, overall mortality and bladder cancer specific mortality rates were also measured.

Univariate Cox regression was performed to evaluate for any clinical predictors of recurrence. Kaplan-Meier curves were used to ascertain probability of treatment success in patients. The log rank test was used to identify statistical differences between stratified groups. The above statistical protocols were used to analyze overall survival and bladder cancer specific survival as well.

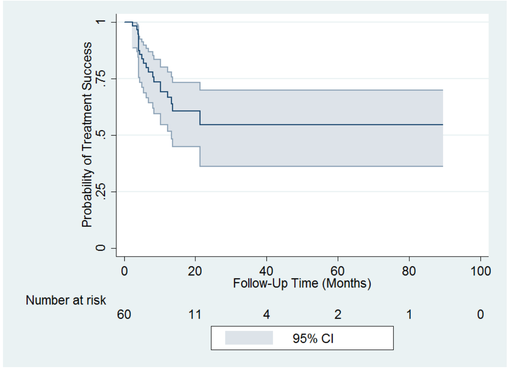

Figure 1: Kaplan-Meier plot of treatment success with GEM/DOCE in patients with NMIBC (n=60)

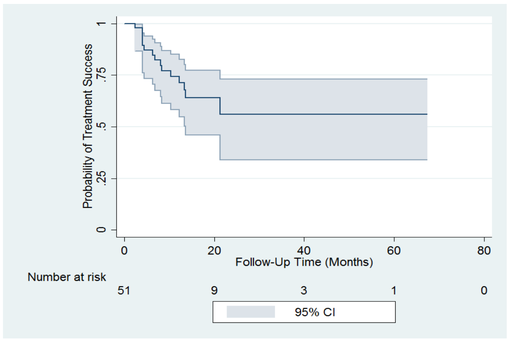

Figure 2: Kaplan-Meier plot of treatment success with GEM/DOCE in patients with NMIBC who failed BCG therapy (n=51)

Results: Treatment Success

Overall treatment success was 83% (50/60) at first surveillance, 69% at 1-year, and 55% at 2-years after induction of GEM/DOCE (Fig. 1). The median follow-up for treatment success was 14.9 months (range 1.9–89.4 months). In those who failed therapy (n=21), median time to failure was 6.1 months (range 2.4–21.4 months). **Treatment success in those who failed BCG therapy (cohort minus BCG naïve) was 90% (53/51) at first surveillance, 74% at 1-year, and 56% at 2-years** after induction of GEM/DOCE (Fig. 2).

Results: Clinical Predictors of Recurrence

A total of 20 patients (33%) had a recurrence of their NMIBC. Patients who underwent more BCG maintenance instillations prior to GEM/DOCE were less likely to recur after GEM/DOCE (p=0.048, HR 0.91). Prior BCG/IFN treatments were also significant (p=0.046, HR 8.64). **Lastly patients who underwent more total GEM/DOCE instillations were less likely to recur (p=0.015, HR 0.86).** Age (p=0.064) and total number of BCG instillations (0.078) were close to being significant.

Variables	No Recurrence N=40	Yes Recurrence N=20	HR (95% CI)	P-value
Age at GEM/DOCE induction (mean, SD)	74.2 (11.0)	69.6 (7.21)	0.95 (0.91, 1.00)	0.064
Gender (male, %)	32 (80.0)	15 (75.0)	0.58 (0.21, 1.63)	0.31
Race (Caucasian, %)	36 (90.0)	18 (90.0)	1.10 (0.25, 4.79)	0.89
Marital Status (Married, %)	30 (75.0)	18 (90.0)	2.38 (0.55, 10.3)	0.24
Smoking Status (yes, %)	28 (70.0)	14 (70.0)	1.40 (0.53, 3.67)	0.48
Pack years (mean, SD)	33.2 (27.9)	31.8 (32.2)	0.99 (0.97, 1.02)	0.77
Number of BCG Maintenance Courses (mean, SD)	1.49 (1.78)	0.93 (1.27)	0.76 (0.53, 1.11)	0.16
Number of Total BCG Maintenance Instillations (mean, SD)	**12.9 (5.93)**	**10.5 (4.82)**	**0.91 (0.83, 0.99)**	**0.048**
Prior BCG/IFN Treatments (yes, %)	**1 (2.50)**	**1 (5.00)**	**8.64 (1.03, 71.8)**	**0.046**
Other Prior Treatments (yes, %)	8 (20.0)	4 (20.0)	0.81 (0.26, 2.45)	0.71
Number of Total BCG Maintenance Courses (mean, SD)	1.51 (1.77)	0.93 (1.28)	0.76 (0.53, 1.10)	0.16
Total Number of BCG Instillations (mean, SD)	13.2 (5.95)	10.9 (5.19)	0.92 (0.84, 1.01)	0.078
Number of Positive Prior Bladder Pathology (mean, SD)	3.25 (1.66)	3.35 (2.11)	1.01 (0.79, 1.26)	0.96
Duration for GEM/DOCE Induction (mean, SD)	6.08 (0.65)	6.15 (0.59)	1.19 (0.65, 2.17)	0.56
Number of Total GEM/DOCE Instillations (mean, SD)	**10.8 (3.87)**	**9.55 (3.87)**	**0.86 (0.76, 0.97)**	**0.015**

Table 1: Characteristics of patients who received GEM/DOCE for NMIBC stratified by recurrence status

Results: Survival Analysis

All-cause and bladder cancer-specific survival were both 97.9% at 1-year (Fig. 3). At 2-years, all-cause and bladder cancer-specific survival were 85.9% and 94.6% respectively. Three (5%) patients who completed GEM/DOCE underwent progression to metastatic disease. They passed away at 9 months, 10.2 months, and 16.7 months after GEM/DOCE induction respectively.

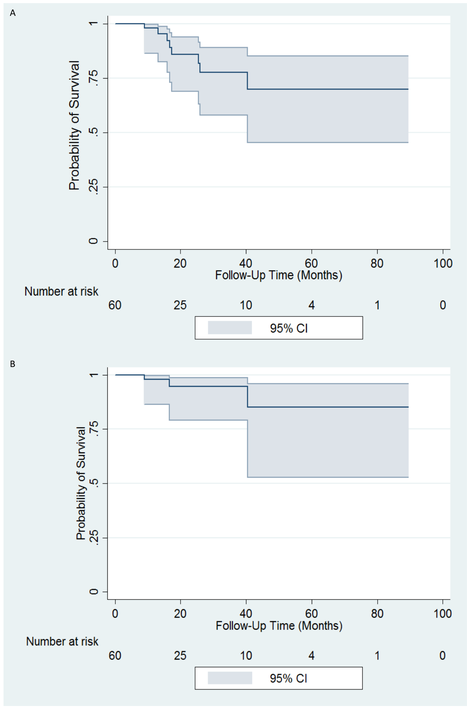

Figure 3: Kaplan Meier plots of A) All- cause survival and B) Bladder cancer-specific survival in patients with NMIBC treated with GEM/DOCE

Discussion and Conclusions

Hyperthermic GEM/DOCE seems to be a well-tolerated salvage regimen that demonstrates a reasonable efficacy and meets the criteria for new therapies for NMIBC set by the FDA and AUA in 2014. Our results show success rates higher than previously published studies. As such, GEM/DOCE warrants further investigation in a prospective, controlled manner to optimize a protocol for patients who remain a challenge to treat.

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