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Nimotuzumab with Concomitant Chemoradiation as an Organ Preservation Treatment in Advanced Muscle Invasive Bladder Cancer

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Abstract

Introduction: Radical Cystectomy (RC) and lymph node dissection is standard of care in MIBC. Bladder preservation techniques like trimodal therapy (TMT) has shown similar outcomes to RC with a complete response (CR) rate of 64-74%, 5 year overall survival (OS) rate of 50-70% along with 40-60% of bladder preservation. As bladder cancers show EGFR overexpression, anti-EGFR can be a potential treatment option in improving outcomes.

Method: We retrospectively evaluated Nimotuzumab with concomitant chemoradiation (CRT) in Muscle invasive advanced bladder cancer (MIBC). Effectiveness and safety outcomes were analysed in these patients.

Results: Sixteen patients with a transitional cell carcinoma and mean age of 63.8 (±4.4) were included Majority of the patients were male (87.5%) and 87.5% patients had tobacco addictions. All patients had an Objective Response Rate (ORR) (15 complete response and 1 partial response). With a median follow up duration of 61 months, median OS and Disease Free Survival (DFS) was not reached. DFS & OS rate of 1, 3, 5 and 7 year was 100% & 100%, 93.8% & 93.8%, 81.3% & 93.8% and 81.3% & 87.5%, respectively. Two patients had metastasis and one patient had recurrence. Two deaths were reported. Only two RC were performed subjecting an organ preservation rate of 87.5%. There were no grade 3/4 AEs recorded.

Conclusion: Nimotuzumab with concomitant CRT improves outcomes with manageable toxicity and can play a potential role as bladder preservation treatment option.

Keywords: Anti-EGFR; Bladder Cancer; Chemoradiation; MIBC; Nimotuzumab; Organ Preservation.

Introduction

India is ranked sixth for incidence of bladder cancer globally. With an age standardized rate (ASR) of 1.6, incidence of bladder cancer constitutes to around 2% (21,096) of all cancers. It has a 5 year prevalence of 49,257, with 11,154 patients dying each year. It is found to be 3.73 times more common in men than in women. It is estimated that there will be a 71.2% increase in the new number of cases each year by 2040.[1] Mean age at presentation of the disease is around 59-60 years with Transitional cell carcinoma (TCC) being the most common histological type.[2,3]

With 5 year survival rate >88%, majority of the patients (70%) account for non muscle invasive bladder cancer (NMIBC). In remaining 30% patients the tumor invade past the bladder submucosa/ mucosa and are known as muscle invasive bladder cancer (MIBC). In addition to which 10-20% of NMIBC eventually progress to MIBC. Such cases are associated with higher risk of metastasis and

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death.[4,5] Radical Cystectomy (RC) and lymph node dissection is standard of care in MIBC. Neoadjuvant cisplatin based chemotherapy is also recommended for eligible patients. Bladder preservation alternatives are employed in patients where cystectomy is not contemplated either for clinical or personal reasons. Concurrent chemoradiation (CRT) is the mainstay in these patients.[6]

Epidermal growth factor receptor (EGFR) is considered as a marker of poor prognosis and has been shown to have abnormal expression in many cancers.[7] EGFR overexpression is seen in up to 74% of bladder cancer tissue specimens and is more common and occurs more frequently in MIBC than in NMIBC.[8,9] Prior research has shown that EGFR overexpression has been associated with bladder progression and poor clinical outcomes.[10,11]

Nimotuzumab is an anti EGFR humanized monoclonal antibody. In India, it is approved in head and neck cancer and has shown to improve outcomes in concurrent with chemoradiation in locally advanced cases.[12] In this study, we have retrospectively evaluated the potential use of Nimotuzumab with concomitant CRT in MIBC in improving clinical outcomes and as a bladder preservation treatment option.

Materials Andmethods

Data was extracted from hospital records retrospectively from 2014-2017 at a government hospital in Jabalpur. Analysis was performed in May 2021, patients continue on follow up till date. Information on tumor and patient characteristics, treatment, response and follow up were collected and analysed. Tumor was staged using American Joint Commission on Cancer (AJCC) 8th Edition. Patients with histologically confirmed MIBC; ≥ 18 years of age; treated with Nimotuzumab (200mg; ≥6 cycles) with concomitant CRT were included in this analysis. Patients having recurrent or metastatic disease; prior cystectomy; treated with prior anti-EGFR therapy were excluded.

Parameters evaluated

Tumor response was evaluated 4 weeks post treatment based on response criteria in solid tumors (Recist 1.1). Disease free survival (DFS) was defined as time from start of treatment till disease recurrence or metastasis. Overall Survival (OS) was defined as time from start of treatment till death. Adverse events (AE) were evaluated based on Common Terminology Criteria for Adverse Events (CTCAE) 4.0. Attempts were made to follow up with patients for survival data. Patients who were lost to follow up were censored.

Statistical Analysis

Basic statistics was applied for the analysis. Kaplan Meir plots for DFS and OS were drawn using SAS 9.4.

Results

Patient Characteristics

A total of 16 patients were included with a mean age of 63.8 (±4.4). All patients had transitional cell advanced MIBC. Majority of the patients were male (87.5%), tumor size T ≥3 (81.4%) and 87.5% patients had different forms of tobacco addictions. Table 1 shows the patient and tumor characteristics.

Table 1: Patient and Tumor Characteristics.

Age		
Mean (± SD)	63.8 (± 4.4)	
Gender		
Male	14	87.5%
Female	2	12.5%
Addictions		
Tobacco	6	37.5%
Smoking	6	37.5%
Nash Manjan	1	6.3%
Gutka	1	6.3%
Alcohol	1	6.3%
None	1	6.3%
Comorbidities		
Diabetes	4	25.0%
Hypertension	5	31.3%
Diabetes and Hypertension	2	12.5%
Hypothyroid	1	6.3%
Stroke	1	6.3%
Breast Cancer	1	6.3%
No Comorbidity	6	37.5%
Tumor Stage		
Stage II	3	18.8%
Stage IIIA	12	75.0%
Stage IIIIB	1	6.3%
TNM Stage		
T2N0	3	18.8%
T3N0	8	50.0%

T3N1	3	18.8%
T3N2	1	6.3%
T4N0	1	6.3%
Histopathological Grade		
Grade II	4	25%
Grade III	12	75%
Number of Lesions		
Single	13	81.3%
Multiple (> 1)	3	18.8%

Treatment

All patients were treated with Nimotuzumab 200 mg in concomitant with cisplatin (40 mg/m2 weekly) and 3-dimensional conformal radiation therapy (3D-CRT) of 60 Gy (2Gy/day for 5 days a week, with a total of 30 sessions) (50 Gy to bladder and nodal region and 10 Gy as boost for bladder). Average number of Nimotuzumab cycles was 6.9 (±0.33). Four patients who had nodal involvement were given 2 cycles of Gemcitabine (1250 mg/m2) and Carboplatin (AUC 5) as induction chemotherapy (ICT).

Response Rate

All patients (100%) had an objective response rate (ORR), of which 15(93.8%) patients had complete response (CR) and one patient (6.3%) showed partial response (PR) after treatment with Nimotuzumab with concomitant CRT.

Disease Free Survival (DFS) and Overall Survival (OS)

The median follow up duration was 61 (Range: 23-84) months. Median DFS and OS was not reached (Figure 1 and 2).

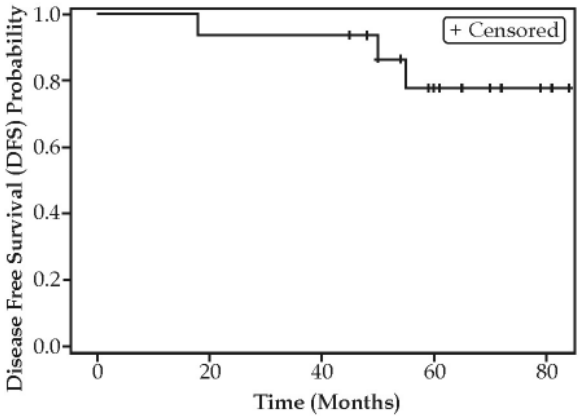

Fig. 1: Disease Free Survival (DFS) Kaplan Meir Plot

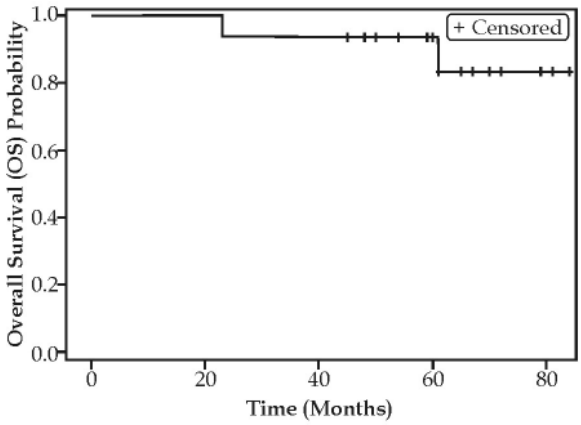

Fig. 2: Overall Survival (OS) Kaplan Meir Plot.

DFS rate of 1, 3, 5 and 7 year was found to be 100%, 93.8%, 81.3% and 81.3%, respectively. OS rate of 1, 3, 5 and 7 year was found to be 100%, 93.8%, 93.8% and 87.5%, respectively.

Safety

A total of 29 AEs were recorded (93.1 % Grade 1 and 6.9% Grade 2) (Table 2). There were No Grade 3 and Grade 4 AE recorded.

Table 2: Adverse Events (AEs).

Adverse Event (AE)	Grade 1	Grade 2
Neutropenia	4	0
Mucositis	2	0
Vomiting	7	0
Loose Motion	9	2
Skin Reactions	5	0
Total	**27**	**2**

Discussion

RC with or without neoadjuvant chemotherapy has been the mainstay in treatment of MIBC. However, morbidity and mortality with this option remain a concern.[13] It can also have a significant impact on quality of life (QoL) with urinary diversions leading to an altered body image, and genitourinary or sexual dysfunction.[14,15]

Recently, organ preservation strategies are being employed to delay if not prevent RC. CRT following transurethral resection of the bladder tumor (TURBT), named trimodal therapy (TMT) has shown similar outcomes with better QoL.[15,16] TMT has demonstrated a CR rate of 64-74%, 5 year overall survival rate of 50-70% along with 40-60% of bladder preservation. Patient selection is crucial for employing bladder preservation treatment as CRT non responders show lower survival

compared to compared to CRT responders. Patients with large tumor size (>5 cm), locally advanced stage (≥ T3), multifocal disease, and the presence of hydronephrosis are shown to have unfavorable CRT response.[17]

EGFR signalling has been shown to regulate the cell proliferation, apoptosis, angiogenesis, invasion, and tumor metastasis observed in preclinical models of transitional cell carcinoma of the bladder.[18] About two thirds of advanced MIBC display EGFR overexpression and is correlated with primary tumor stage, recurrence, progression and patient survival.[19] Several anti EGFR tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (MAbs) have been evaluated as potential treatment option.

Geftinib, in a phase 2 study was combined with gemcitabine and cisplatin in the treatment of advanced urothelial carcinoma. The outcomes of the study showed an ORR of 42.6%, median OS of 15.1 months and median time to progression of 7.4 months. Addition of geftinib did not seem to improve outcomes compared to only chemotherapy.[20] A phase 2 study evaluated erlotinib as neoadjuvant therapy before RC in MIBC. At surgery, it was found that 25% patients had pT0 and 35% were down staged to pT1 or less. Half of the patient population (50%) were alive at a median follow up duration of 24.8 months.[21] The dual EGFR and HER2 inhibitor, laptinib, has mostly been evaluated as a second line or maintenance therapy in metastatic disease.[22-24] EORTC 30061, phase 1 trail, evaluated maximum tolerated dose of lapatinib with gemcitabine and cisplatin in advanced urothelial carcinoma. With an ORR of 59%, 1,250mg of laptinib was determined as the maximally tolerated dose with this combination.[25] Cetuximab combined with paclitaxel in previously treated metastatic urothelial cancer showed an ORR of 25%, median PFS of 16.4 weeks and median OS of 42 weeks.[26] A phase 1/2, single arm, study evaluated cetuximab with 5FU and Mitomycin C or cisplatin with concurrent radiotherapy in MIBC. Three month pathological CR rate of 88%, five local progressions and four deaths were reported. Local control at 3 months was 77%; 12 month muscle invasive loco regional progression free survival (LPFS) was 93%, metastatic free survival of 90% and OS of 87%. Twelve patients (43%) reported at least one significant AE, grade 4 toxicities observed were dyspnea, atrial fibrillation, interstitial pneumonitis, sepsis, thromboembolism, neutropenia and palpitations. The most common grade 3 AE were skin rash, diarrhoea, low platelet count, low white blood cell count, fever and haematuria.[27,28] Panitumumab with concurrent RT after induction chemotherapy and lymph node dissection in MIBC was evaluated by Fransen van de Putte EE et al.[29] CR was achieved in 29 of 31 patients (94%) and at a median follow up of 34 months, 4 patients had recurrence and 3 (10%) underwent RC. However, 16% patients experienced grade 3/4 AE and four patients discontinued treatment due to toxicity. While more research is warranted, anti-EGFR treatment has a potential role as bladder preservation technique in MIBC.

In this study, we retrospectively evaluated Nimotuzumab with concomitant CRT in MIBC in terms of effectiveness and safety. Similar to historical studies, patients in this study were of old age (mean=63.8), having tobacco addictions (87.5%) and majority were male (87.5%). Most of the patients (81.4%) had tumor size T ≥3. Four patients had nodal disease where 2 cycles of prior ICT was given. All patients (100%) had ORR (15 CR and 1 PR). With a median follow up duration of 61 months, DFS & OS rate of 1, 3, 5 and 7 year was 100% & 100%, 93.8% & 93.8%, 81.3% & 93.8% and 81.3% & 87.5%, respectively. Higher-grade bladder malignancies have tendency of local or distant invasion most commonly in lymph nodes, lungs, bone or liver. In our study, two patients had lung metastasis at 18 and 55 month, both of them had multiple lesions, grade III, large tumor size (T3) and the latter had nodal disease (N2). These two patients died at 23 and 61 months, respectively. Employing ICT in such patients followed by Nimotuzumab with CRT can potentially prevent or delay metastasis and disease spread, thereby improving survival time as seen in the second patient. Only two patients (12.5%) underwent RC, which shows that this treatment can be a potential bladder preservation treatment option with an organ preservation rate of 87.5%. One patient who had T3N1 tumor attained a PR and hence RC was performed. The patient showed good response after surgery and was disease free and alive till 48 months of follow-up. The second patient also had a T3N1 tumor, with primary recurrence at 50th month underwent RC. The patient showed good response after surgery and was disease free and alive till 67 months of follow-up. Even though it was observed that patients with high tumor size and nodal involvement subsequently required a RC, Nimotuzumab with CRT does seem to play a role in improving long term survival. There were no grade 3/4 AEs recorded. A total of 29 AEs (93.1 % Grade 1 and 6.9% Grade 2) were recorded which were manageable.

To the best of our knowledge, this is the first

report on use of Nimotuzumab with concomitant CRT in advanced MIBC. Apart from its retrospective nature, limitations of this study include small sample size, single centered and single arm study. Further research in terms of controlled trials is warranted to verify these results and to analyze patient selection criteria for anti-EGFR treatment.

Conclusion

Nimotuzumab with concomitant CRT improves outcomes with manageable toxicity and can play a potential role as bladder preservation treatment option.

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