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Review article

Interferon alfa in the treatment paradigm for non–muscle-invasive bladder cancer

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Abstract

Objectives: In this article, we review the various options for and the potential role of interferon alfa (IFN-α) in the treatment of non–muscle-invasive bladder cancer (NMIBC).

Methods: PubMed was searched for journal articles on IFN-α use in treating bladder cancer. The references listed in the National Comprehensive Cancer Network guidelines were used as a guide to identify relevant publications on treatments for NMIBC.

Results: Transurethral resection with adjuvant intravesical chemotherapy or immunotherapy is the standard treatment option for NMIBC. Adjuvant IFN-α therapy has limited efficacy in preventing recurrences in intermediate-risk and high-risk patients; bacillus Calmette-Guérin (BCG) monotherapy is the recommended first-line treatment in these patients. Unfortunately, cancer progression or recurrence is a common outcome; radical cystectomy, which is often the lifesaving approach in such a scenario, is associated with significant morbidity, mortality, and decreased quality of life. Current alternatives to cystectomy include repeat intravesical immunotherapy, conventional instillation chemotherapy, and device-assisted intravesical chemotherapy. The efficacy of any chemotherapy after BCG failure, either conventional or device assisted, has not been established. BCG and IFN-α combination intravesical therapy has not been investigated thoroughly; based on available data, combination therapy appears to be most effective in patients with carcinoma in situ and may be preferentially considered as an alternative to radical cystectomy for patients with intermediate-risk or high-risk NMIBC who do not tolerate the standard BCG dose or experience BCG failure after 1 year of therapy. However, this approach requires close follow-up and should only be chosen after careful consideration of all risk factors.

Conclusions: There is a lack of efficacious treatment options for patients with NMIBC recurrence or progression after initial BCG treatment. There is a need for well-designed clinical trials investigating the safety and efficacy of available therapies, including BCG and IFN-α2b combination therapy.

Keywords: Non–muscle-invasive bladder cancer; Interferon alfa; Bacillus Calmette-Guérin; Immunotherapy; Chemotherapy; Intravesical therapy

1. Introduction

Urothelial carcinoma (UC) of the bladder is the most common neoplasm of the urinary system, with an estimated 73,510 new cases and 14,880 deaths projected in the United States for 2012 [1]. Most patients with bladder cancer have non–muscle-invasive bladder cancer (NMIBC) at first diagnosis, which is treated with transurethral resection (TUR), followed by intravesical chemotherapy or immunotherapy to prevent recurrence and progression [2]. The probability of recurrence of NMIBC (Ta/T1) at 5 years ranges from 31% to 78%, with the probability of progression at 5 years being as high as 45% in high-risk patients (defined as those with high-grade tumors, carcinoma in situ [CIS], and T1 NMIBC) [2,3]. Patients with CIS have an approximate 5-year recurrence rate of 50% to 90% and face the highest risk of disease progression [4].

In this article, we review the various treatment options for NMIBC and the potential role of interferon alfa (IFN-α) in its treatment. A PubMed search for journal articles reporting on the use of intravesical IFN in treating bladder

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cancer (end date, July 2012) yielded 50 results. These were reviewed for relevance (i.e., clinical studies regarding the therapeutic role of IFN-α in the United States or Europe). In addition, the National Comprehensive Cancer Network guidelines were used as the starting point for the identification of key papers on the treatment of NMIBC [4]. When appropriate, references cited in these papers were also reviewed.

2. IFN-α monotherapy

IFN-α is a pleiotropic immune modulator that has demonstrated antiproliferative activity in preclinical studies. Initial early-phase clinical studies (1) indicated that intravesical IFN-α monotherapy may elicit significant tumor responses in patients with high-risk NMIBC, including those with CIS. In a dose-escalation study by the Northern California Oncology Group, 16 patients with grade 1 or 2 recurrent UC, 19 patients with primary or recurrent CIS, and 2 patients with severe dysplasia received intravesical IFN-α2b of 50 MU to 1,000 MU for 8 weeks. Four patients (25%) with UC and 6 patients (32%) with CIS or severe dysplasia had a complete response at week 12 [5]. Complete responses were obtained at all dose levels. Even high doses had no major systemic adverse effects and the maximum tolerated dose was never reached [5]. In a subsequent multicenter randomized trial of intravesical IFN-α2b of 10 MU or 100 MU administered weekly for 12 weeks and subsequently monthly for 12 months in 85 patients with CIS, 43% of those receiving the high dose ($n = 47$) had a complete response, compared with 5% receiving the low dose ($n = 38$; $P < 0.0001$). Complete responders included 2 patients in the high-dose group with relapse after previous therapy [6]. Similarly, in a marker lesion study in 115 patients with primary or recurrent Ta/T1 grade 1 or 2 UC, complete response rates of 19%, 33%, and 41% were obtained after 12 weeks of treatment with IFN-α of 30 MU, 50 MU, and 80 MU, respectively. However, all of these rates were significantly lower than the complete response rate (72%; $P < 0.05$) observed in a control group of patients treated with mitomycin C (MMC) [7].

A number of randomized controlled studies evaluated the efficacy of adjuvant IFN-α monotherapy in preventing recurrence in intermediate-risk patients (those with multiple or recurrent low-grade tumors) [8,9] and high-risk patients (Table 1). In a dose-finding study in 89 patients with recurrent Ta/T1 UC grade 2, 6-month monotherapy with IFN-α2b of 60 MU or 80 MU was associated with significant reductions in 36-month recurrence rates compared with TUR alone ($P < 0.05$) [10]. However, in a double-blind, placebo-controlled study in 90 patients with primary or recurrent T1 tumors, IFN-α2b of 60 MU administered once weekly for 12 weeks and subsequently monthly until completion of 1 year had no significant prophylactic effect at 43 months of mean follow-up [9]. Results of other randomized controlled studies further showed that IFN-α2b of 50 MU is inferior to MMC of 40 mg as prophylaxis in patients with intermediate-risk NMIBC (primary Ta grade 2 or T1 grade 1 or 2) [12] and is ineffective in preventing recurrence in patients with primary T1 UC when administered as immediate single postoperative instillation [13]. In addition, IFN-α2a of 54 MU has been shown to be inferior to bacillus Calmette-Guérin (BCG) as immunoprophylaxis in patients with recurrent T1 UC [14].

In conclusion, IFN-α2b at doses of 50 MU to 100 MU elicits moderate antitumor responses in patients with CIS or UC, but has limited efficacy as adjuvant monotherapy in preventing recurrence in intermediate-risk to high-risk patients. Although IFN-α2b is well tolerated at doses up to 1,000 MU, doses higher than 100 MU have not been evaluated in randomized controlled trials, and thus, there is no evidence that they would provide greater benefit. It should be noted that most of the research in NMIBC has been conducted with the 2b form of IFN-α compared with IFN-α2a.

3. BCG monotherapy

BCG is a first-line option for patients with intermediate-risk NMIBC [8,9]. It is also recommended as second-line therapy for intermediate-risk patients who failed intravesical chemotherapy and as first-line therapy for all high-risk patients [2,3,9,15]. For patients with CIS, complete response rates with BCG are ~70% [16], with some studies reporting >80%, with the use of BCG maintenance regimens [17,18].

BCG immunotherapy after TUR significantly reduced the risk of tumor recurrence [2]. A number of randomized controlled clinical trials and meta-analyses further demonstrated that the benefit of BCG immunotherapy increases significantly with the use of maintenance therapy, especially if BCG is given weekly for the first 6 weeks, then weekly for 3 weeks at months 3 and 6, and then every 6 months for 3 years [8,17,19]. Recently, the European Organisation for Research and Treatment of Cancer 30962 study investigated the differences in efficacy with full dose vs. one-third of the standard dose (1/3-dose) of BCG as well as with 3 years of maintenance vs. 1 year of maintenance in 1,355 patients with intermediate-risk and high-risk NMIBC after TUR [20]. While the prespecified criteria for superiority of full dose vs. 1/3-dose BCG and 3 years vs. 1 year of maintenance were not met, the 5-year disease-free interval rates were 54.5%, 58.8%, 62.6%, and 64.2%, respectively, for the 1/3-dose—1-year maintenance, full dose—1-year maintenance, 1/3-dose—3-year maintenance, and full dose—3-year maintenance. BCG therapy when used for 3-week maintenance has been found in multicenter randomized trials to reduce stage progression [19–22].

Although the introduction of BCG therapy constituted a major advancement in the treatment of intermediate-risk and