Inflammation and Urothelial Bladder Cancer: What we Need to Known? (Review)

Tommaso Cai[1,*], Gabriella Nesi[2], Sandra Mazzoli[3], Francesca Meacci[3], Galliano Tinacci[4], Cesare Selli[5] and Riccardo Bartoletti[6]

[1]*Department of Urology, Santa Chiara Regional Hospital, Trento, Italy*

[2]*Division of Pathological Anatomy, Department of Critical Care Medicine and Surgery, University of Florence, Italy*

[3]*STDs Center, Santa Maria Annunziata Hospital, Florence, Italy*

[4]*Department of Pathology, Santa Maria Annunziata Hospital, Florence, Italy*

[5]*Department of Urology, University of Pisa, Italy*

[6]*Department of Urology, University of Florence, Italy*

Abstract: The association between inflammation and bladder cancer has been debated in several studies, highlighting that inflammation may be a crucial component both in tumor development or progression. On the other hand, several authors suggest that the presence of an inflammatory cell infiltrate within the urothelial bladder cancer is a good prognostic predictor in terms of recurrence-free survival time. The question is: What is the prognostic role of inflammation in patients affected by urothelial bladder cancer? On one hand, chronic inflammation should be considered a risk factor in developing bladder cancer, as demonstrated by *Schistosoma haematobium* infection and, on the other hand, the inflammation induced by the Bacillus Calmette-Guérin intravesical therapy has a protective effect on cancer recurrence. Recently, some authors highlight that the presence of an inflammatory cell infiltrate within the urothelial bladder cancer is a good prognostic predictor in terms of recurrence-free survival time, due to the host generating angiogenic stimulation of a local inflammatory reaction against cancer. This is probably due to the angiogenetic stimulation of a local inflammatory reaction generated by the host against superficial bladder cancer. However, the debate is still open. This review will summarize recent data regarding inflammation and urothelial cell carcinoma, with special emphasis on the role that the inflammatory response is likely to have on recurrence risk and progression in superficial bladder cancer patients.

Keywords: Interleukins, bladder cancers, urothelial cancer, flogosis, inflammation.

1. INTRODUCTION AND EVIDENCE ACQUISITION

The association between inflammation and cancer has been pointed in epidemiological and clinical studies, showing that chronic inflammation may contribute to carcinogenesis in several types of malignancy, such as esophageal, pancreatic, and gallbladder carcinomas [1-2]. There is not unanimity in the current literature in the assessment the prognostic role of inflammation in bladder cancer patients. Some authors suggest that chronic inflammation should be described as a cancer promoter, since tumor inflammation reaction can facilitate the breakage of the basement membrane, a process required for tumor cells to migrate, invade and metastasize [3-4]. Contrariwise, some studies indicated that the presence of an inflammatory cell infiltrate within the bladder tumor is a good prognostic predictor in terms of recurrence-free survival time, owing to the host generating angiogenic stimulation of a local inflammatory reaction against cancer [5-6]. Moreover, on one hand, chronic inflammation should be considered a risk factor in developing bladder cancer, as demonstrated by *Schistosoma haematobium* infection and, on the other hand, the inflammation induced by the Bacillus Calmette-Guérin (BCG) intravesical therapy has a protective effect on cancer recurrence [7-8]. Furthermore, a large variety of pro-inflammatory cytokines, such as IL-6, TNF, COX-2, VEGF and iNOS, are expressed by bladder cancer and immune cells, bind to specific receptors and activate distinct signal pathways to transcriptionally activate a plethora of downstream factors [9-11]. The fact that an inflammatory reaction occurs more frequently in superficial rather than invasive carcinomas prompts the hypothesis of a substantial deficiency in the host immune response to muscle invading tumors. Here, we aimed to summarize recent data regarding inflammation and urothelial cell carcinoma, with special emphasis on the role that the inflammatory response is likely to have on recurrence risk and progression in superficial bladder cancer patients. We conducted a search of the English-language literature from 1960

*Address correspondence to this author at the Department of Urology, Santa Chiara Hospital, Trento, Largo Medaglie d'Oro 9, Italy; Tel: +39 0461 903306; Mob: +39 3339864943; Fax: +39 0461 903101; E-mail: ktommy@libero.it

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through December 2010 with use of the Medline computerized database of the US National Library of Medicine (http://www.ncbi.nlm.nih.gov/pubmed). The Medline search has been carried-out by using the following Medical Subject Headings and free text terms: inflammation and bladder neoplasms (exploded) were combined with the terms prognosis, recurrence, progression, outcome and then limited to humans and male. Moreover, we searched reference lists of articles to identify potential additional references. All original paper and review studies on bladder cancer have been considered for this review. We considered also guidelines from the National Institute for Health and Clinical Excellence, the European Association of Urology and the American Urological Association recommendation on bladder cancer. From an initial literature search with 81 unique citations, a total of 40 articles were selected for the present review. A matched research between inflammation and bladder cancer (exploded) and outcome and/or recurrence and/ore progression has found 36 articles.

2. STARTING FROM CLINICAL EVIDENCE

Epidemiological data suggest that infection and chronic inflammation have been recognized as important risk factors for carcinogenesis and malignancies and approximately 18% of cancer cases worldwide are attributable to infectious diseases caused by bacteria, viruses, and parasites [12]. On the other hand, several studies have shown that tumor is potentially immunogenic and that the host immune response influences survival [1]. It has emerged that bladder carcinoma is a particularly good example of immune-associated cancer. In 1979, Mihatsch *et al*. found that patients with invasive bladder carcinoma reported a significantly better 1-year survival when lymphocytes, plasma cells and/or lymph follicles were present in the tumors [13]. The Authors, for the first time, highlighted the significant prognostic value of lympho-plasmocytic inflammation as local expression of immunological host resistance [13]. From this evidence, a new research field has been raised: the prognostic role of tumor-associated inflammation.

The new field of research has been based of two scientific backgrounds:

- the reported effect of Coley's toxin on cancer [14]

- the anti-tumor effects of inflammation by inducing a local immune response to Bacillus of Calmette and Guerin instillations into the bladder in patients with urothelial tumours, due to the massive influx of cytokines and inflammatory cells into the bladder mucosa [15-16].

Coley WB in 1891, for the first time, injected streptococcal organisms into a patient with inoperable cancer with success. He thought that the infection he produced would have the side effect of shrinking the malignant tumor [14]. This was the first example of immunotherapy against cancer. Moreover, the fact that inflammation plays a primary role in host reaction to the tumor has also been widely emphasized in other neoplasms, such as colon or stomach cancer [17-18]. In stomach cancer, particularly, natural killer (NK) cell activity has been identified as an independent parameter of good prognosis, in patients undergoing gastric resection [18], due to the natural cytotoxicity, mediated by NK cells, inhibiting cancer cell growth [18].

3. CLINICAL EVIDENCE IN BLADDER CANCERS

The role of immune mechanisms in the pathogenesis and spread of bladder cancer has been debated for many years. Several authors found that tumor-associated cell infiltration was associated with good prognosis in patients with non-muscle invasive bladder cancer (NMIBC) [3-4]. Offersen *et al*. demonstrated an independent prognostic value of intense inflammation in predicting favorable outcome in patients affected by muscle invasive urothelial carcinoma, highlighting that host generates a local response against bladder cancer, in terms of inflammatory reaction, modifying tumor natural history and its clinical behavior [19]. Moreover, Flamm demonstrated in a cohort of patients with primary NMIBC that patients with an inflammatory reaction in their tumor experienced significantly fewer recurrences and cancer-related deaths compared to those with tumors without inflammation [3]. On the other hand, Lipponen *et al*. found that CD3+ T cells in NMIBC predicted the progression of tumors and the related short recurrence-free survival [5]. The same results have been reported by Krpina *et al*. that found differences in the number of tumor infiltrating lymphocytes (TILs) between the group of patients with recurrence and the group of patients without recurrence at the time of initial transurethral resection of bladder tumors [6]. Particularly, they found significantly fewer infiltrating CD3+ and CD8+ T cells in sample of NMIBC from patients without recurrence than those with recurrence, highlighting that that CD3+ T cells in NMIBC predicted the progression of tumors

and the related short recurrence-free survival [6]. The authors hypothesized that poor prognosis related to the presence of TILs may be due to the inhibitory mediators released by the tumor cells [5-6]. These results are in contrast to the findings obtained by other authors, who reported good prognosis for the patients with higher number of TILs, such as Tsujihashi *et al*. that highlight the role of local immunosurveillance directed against bladder tumors [20]. There are, then, different literature findings regarding prognostic significance of tumor infiltrating lymphocytes. As suggested by Krpina *et al*. these different literature findings can been explained by heterogeneity of the analyzed bladder cancers (NMBIC and muscle-invasive ones) or by the use of different methodologies for TILs quantification and the lack of a different T cell subtypes analysis [6].

4. FROM THE BENCH TO THE BEDSIDE

Several authors suggested that Vascular Endothelial Growth Factor (VEGF) probably mediates the link between tumor-associated inflammatory infiltration and good prognosis in bladder cancer, highlighting the role of activated polymorphonuclear cells (PMNs), founded in TILs, can release VEGF from intracellular stores and thereby stimulate angiogenesis [21]. In particular, Bartoletti demonstrated that a strong correlation between peritumoral neoangiogenesis and improved survival in non muscele-invasive urothelial carcinoma [11]. They highlighted that this correlation may be due to the angiogenetic stimulation of a local inflammatory reaction generated by the host against superficial bladder cancer [11]. The activation of PMNs with consequent releasing of VEGF and angiogenesis stimulation, should be considered the key of the comprehension of the mechanism of good prognostic impact of inflammation in bladder cancer [6].

Two important fields should be discussed in order to understand it:

- the characterization and role of lymphocytic infiltrate that could represent a specific response by the host against the tumor.

- the role of PMNs, VEGF and angiogenesis.

5. ROLE OF PERI-TUMOURAL LYMPHOCYTIC INFILTRATE

The predominant inflammatory cell types found in bladder cancers were lymphocytes and plasma cells reflecting a chronic inflammatory response to the tumor. However, several Authors encountered a high frequency of polymorphonuclear cells (PMN) reflecting signs of acute inflammation. Here, we have to discuss the role of tumor-associated inflammatory cells and if there is a different impact of chronic or acute inflammatory response to the tumor. It is well known that adjuvant therapy with BCG instillation reduce the recurrence rate by stimulating a local inflammatory response [15-16, 22]. Several studies highlighted the importance of the local inflammatory response, which is characterized by an influx of leukocyte subpopulations, such as granulocytes, CD4 and CD8 T cells and NK cells, and granuloma formation [23]. Moreover, cytokines released by BCG stimulation and considered significant for the antineoplasic response are essentially those related to Th1 (IL-12, IL-2, TNF-α and IFN-γ), while a BCG inhibitory effect is related to the Th2 (IL-10) response [24]. Furthermore, some authors focused their attention on IL-10. IL-10 seems a suppressor of TNF-α synthesis and a potent anti-inflammatory cytokine that is present at the sites of tumors in a wide variety of human cancers, including transitional cell carcinoma of the bladder [24]. Cai *et al*., recently, demonstrated that IL-6 and IL-10 have an important role in regulating the host immune-response against the bladder cancer and the IL-6/IL-10 ratio should be considered as an independent prognostic factor in predicting recurrence in urothelial bladder cancer patients [22]. IL-6 has a fundamental role in support of systemic host response to tissue injury [25-26]. Mulé *et al.* have described an anti-tumor effect of IL-6 in mouse lung cancer, confirming that induction of host immunological response is probably central in reaction against cancer [27]. On the other hand, several studies have demonstrated that IL-10 has the physiological role of down-regulating cell-mediated immunity, resulting in an improvement of tumor immune escape [28]. Recently, Nadler *et al.* have reported that IL-10 is an important modulator of immune mediated events *in vivo* and suggest that efforts to down-modulate this inhibitory cytokine may be of therapeutic value [29]. The fact that IL-6/IL-10 is a good prognostic marker that should be used in clinical practice was based on the following reasons: 1) High IL-10 level, with IL-6/IL-10 decreasing, should be an expression of tumour immunosuppressive action that eliminates the ability of immunocompetent cells to respond to the tumour [28]. 2) IL-10 was reported as a promoter of an immune deregulation, with an enhancement of Th2 cells [29]. Indeed, patients with bladder cancer seem to develop a Th2 dominant status with a deficient type immune response due to an increase in IL-10 levels [29]. The demonstrated

immune deregulation should be proved by an altered IL-6/IL-10. 3) The fact that a decrease of IL-6 levels and an enhancement of IL-10 levels are a demonstration of an altered host immune response to the tumor, is well confirmed by cell activation due to the Bacillus Calmette-Guerin (BCG) [28]. Production of immunosuppressive IL-10 during BCG therapy reduces inflammation and the anticancer response [24]. In addition, the fact that IL-6 and IL-10 are promoters of two different immune response pathways, such as Th1 and Th2 [8], is an evaluation of host immunological response type to the tumor. Zhang *et al*. have demonstrated induction of cytokine production by BCG, particularly IL-6 [30]. Recently, Luo and co-workers have shown the inhibitory role of IL-10 in BCG-induced macrophage cytotoxicity, suggesting that blockage of IL-10 may potentially enhance the effect of BCG in the treatment of bladder cancer patients [31]. Chen has demonstrated that BCG increases IL-6 messenger RNA and protein in a time- and dose-dependent manner *via* an immediate early pathway [32]. On the other hand, several authors highlighted the role of other cytokines in the BCG response, such as IL-2. Particularly, De Boer *et al*. demonstrated that mean IL-2 concentration increased rapidly from the second BCG instillation, suggesting that activation of BCG-specific T cells was indicated by the detection of IL-2 [33]. Watanabe *et al*., moreover, concluded that urinary IL-2 at the eighth instillation of BCG might serve as a valuable prognostic factor of treatment efficacy as well as tumor recurrence after treatment [34].

6. ROLE OF PMNs, VEGF AND ANGIOGENESIS

Many studies have demonstrated that angiogenesis could be considered a prognostic factor in bladder cancer. Most highlighted a correlation between increased vascularization and poor clinical outcome [35]. However, several studies on other neoplasms demonstrated the relation of angiogenesis to survival improvement [36]. VEGF, iNOS and COX-2 are angiogenetic factors, likewise inflammatory cytochines. VEGF is produced by serological or cellular stimulation. Upregulation of iNOS expression induced by IFN-γ after BCG (Bacillus of Camette and Guerin) instillations into the bladder was demonstrated [37]. COX-2 is not expressed by normal vesical tissue but it can be find as angiogenetic factor in bladder cancer like in other neoplasms [38]. A significant COX-2 expression was found in tumor infiltrating cells, in neoplastic cells, in endothelial cells and in fibroblastic cells. Bol *et al*. recently described a lower frequency of skin tumor in transgenic mice with COX-2 overexpression following exposure to carcinogens [39]. Bartoletti *et al*. found a directly proportional increase in VEGF expression and MVD compared to a better prognosis, demonstrating a strong correlation between peritumoral neoangiogenesis and improved survival in NMIBC [11]. This correlation may be due to the angiogenetic stimulation of a local inflammatory reaction generated by the host against superficial bladder cancer, as suggested by Offersen at al. [19]. Those results confirm that angiogenetics citokine expression and inflammation cells inside and around the tumour could be considered a good prognostic factor. In fact, it is probably due to the tumor–host interaction, mediated by angiogenetic cytokines, that has effects on tumour progression by preventing tumour development. In particular, IL-2 is a cytokine described to promote activated T-cell proliferation with an important impact on patient's outcome and survival.

7. CONCLUSION AND FUTURE DIRECTIONS

This review provides a summary of the currently available knowledge about the role of inflammatory reaction in non-muscle invasive bladder cancer. Even if BCG has been shown to reduce the risk of tumor progression and recurrence risk rate, significant proportions of patients do not respond to BCG therapy and 30% to 50% of initial responders have relapse within the first five years [40-41]. Preliminary clinical studies showed no convincing results in terms of recurrence-free rate by using combination therapy with IFN-α plus low dose BCG or IL-2 [42-43], demonstrating that the comprehension of tumor associate inflammatory response could be the key of improve the treatment of patients affected by NMIBC. Although several evidences have been reported about the prognostic role of inflammation and its molecular mediators in patients affected by bladder cancer, the potential of therapies that can modulate the inflammatory tissue against the tumor will likely pave the way for the fight against bladder cancer and promote the development of personalized therapy for early diagnosis and treatment of cancer.

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