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Meta analysis

Concurrent gemcitabine and radiotherapy for the treatment of muscle-invasive bladder cancer: A pooled individual data analysis of eight phase I–II trials

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ABSTRACT

Purpose: Although radical cystectomy is still considered the standard of care for most localized muscle-invasive bladder cancer (MIBC) patients, bladder-sparing strategies with chemoradiotherapy have demonstrated comparable local control and survival rates when adjusting for tumor stage. We present a pooled analysis of individual patient data out of published trials with gemcitabine-based chemoradiotherapy for MIBC.

Methods and materials: Individual patient data were collected from Institutions that enrolled patients into trials that evaluated gemcitabine-based chemoradiotherapy for MIBC.

Results: We identified eight studies published on gemcitabine-based radiochemotherapy and 190 patients were included in this analysis. A complete response (CR) was observed in 166 patients (93%). After a median follow up of 44.5 months, 36 patients (18.9%) presented a bladder recurrence and 14 subsequently underwent cystectomy. The 5-year overall survival (OS), disease-specific survival (DSS), and cystectomy-free survival (CFS) rates were 59%, 80.9%, and 93.3%, respectively. The achievement of CR after chemoradiotherapy was the main prognostic variable which was associated with improved OS, DSS, and CFS. The treatment was well tolerated.

Conclusion: This pooled analysis strengthens the evidence that chemoradiotherapy regimens with concurrent gemcitabine are feasible and well tolerated. Prospective randomized controlled trials are on-going to definitively assess the efficacy of gemcitabine-based chemoradiotherapy for MIBC.

Radical cystectomy is still considered the standard of care for most localized muscle-invasive bladder cancer (MIBC) patients [1]. Bladder-sparing strategies, followed by cystoscopic surveillance and salvage cystectomy in cases of localized recurrence may be an alternative approach in highly selected patients [2]. Bladder preservation, with transurethral resection (TURBT) and external beam radiotherapy (EBRT), has previously been reported to achieve equivalent disease specific survival rates as radical cystectomy of approximately 50% [3–5]. More recently, the use of chemoradiotherapy or other radiosensitization strategies, have demonstrated improved local control and survival rates when it was compared to EBRT alone in phase III studies [6,7]. While there is no randomized controlled trial comparing these strategies to radical cystectomy, results in terms of both local control and overall survival appear to be at least equivalent [8]. Bladder preservation has the added value of a life with one's own functioning bladder which is beneficial in terms of quality of life for many patients [9,10]. Such a strategy may also be followed in selected patients who are not suitable candidates for radical surgery due to co-morbidities. Although historically cisplatin has been considered as the reference radiosensitizer in this setting, there is no internationally agreed standard regimen today.

Gemcitabine is widely accepted as a key chemotherapeutic agent in combination with cisplatin for both the neoadjuvant [11] and the palliative setting [12]. Its radiosensitising activity and favorable toxicity profile makes it an attractive agent for chemoradiotherapy in MIBC [13].

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The reported experiences in other cancers highlighted the risk of unacceptable toxicity when conventional gemcitabine doses are administered concurrently to EBRT, leading to a cautious use of this combination with reduced drug doses [14,15].

To date, the final results of eight phase I–II trials have been published reporting the safety and activity profile of gemcitabine-based concurrent chemoradiotherapy for the treatment of MIBC [16–23]. Although these studies adopted different gemcitabine schedules (alone or in combination with cisplatin) and had some differing eligibility criteria, they confirmed that this chemoradiotherapy combination is a feasible treatment and able to produce a high rate of complete cystoscopic response and promising long term outcomes.

The present report is based on a pooled analysis of individual data, to provide a cumulative assessment of long-term outcomes of the patients who had received gemcitabine concurrently with EBRT as bladder preservation treatment for localized MIBC in the above described published studies.

Patients and methods

Study design and population

The study was designed as pooled analysis of individual data from eight studies published prior to August 30th, 2014: six phase I studies [16–18,21–23] and two phase II studies [19,20].

Each of the respective centers was contacted and asked to provide individual patient data for this analysis. Updated follow-up data were requested whenever possible and available. Original data concerning all patients included in the eight studies were available, while update information were available only for four studies. Each of the studies was reviewed and approved by the reference Institutional Review Board.

The study protocol was set up by the study coordinator, discussed and finally approved by all participating investigators.

Procedures

Each local investigator was responsible for collecting and submitting individual anonymized data, by September 30th, 2014. Data files were manually checked for eligibility and queries were sent to centers as needed. Thereafter, data were merged into a centralized database accessible only to the study coordinator and statistician. Individual patient information on the following data was requested according to the protocol: date of study inclusion, treatment response, survival, local recurrence, metastases and date of last follow-up was sought. We also collected details of age, gender, clinical TNM category, grade, performance status, chemotherapy dosing, administration and toxicity, radiotherapy schedule, dosing and acute and late toxicity. To reduce potential bias, information was requested for all enrolled patients including those who had been excluded from the investigators' original analyses.

No financial compensation was offered to individuals or participating centers.

Statistical methods

Survival probabilities were estimated using the Kaplan–Meier method [24] and the following definitions:

Overall survival (OS): Events were defined as death due to any cause. The time to OS was the interval between treatment initiation and death, or the most recent follow-up if no event occurred.

Disease-specific survival (DSS): Events were defined as death attributable to bladder cancer. The time to DSS was the interval between treatment initiation and death due to bladder cancer, or the most recent follow-up if no event occurred.

Cystectomy-free survival (CFS): Events were defined as cystectomy for any reason. The time to CFS was the interval between treatment initiation and cystectomy, or the most recent follow-up if no event occurred.

Local disease-free survival (LDFS): Events were defined as any superficial or infiltrating bladder cancer relapse. The time to LDFS was the interval between treatment initiation and the first bladder failure, or the most recent follow-up if no event occurred.

Distant disease-free survival (DDFS): Events were defined as distant failure (i.e. metastases). The time to DDFS was the interval between treatment initiation and the occurrence of distant metastases, or the most recent follow-up if no event occurred.

Cox proportional hazards regression model was performed to identify clinical variables associated with OS, DSS, and CFS. The following covariates were included in the analysis: age, sex, T stage (T2 vs T3/T4a), presence of in situ tumor, multifocality of the tumor, presence of hydronephrosis, suitability for surgery (due to large tumor extent or due to co-morbidity), gemcitabine dose, concomitant cisplatin administration, and complete response (CR) at first assessment post treatment completion. A univariate analysis was made and the factors identified as significant were included in the multivariate analysis, which was performed using a backward procedure. All statistical comparisons were two-sided, and $P \leqslant .05$ was considered statistically significant at exploratory level.

All statistical analyses were performed using SPSS 12 software (SPSS Inc., Chicago, IL).

Results

Characteristics of the selected studies

The majority of the studies included patients who were suitable for bladder preservation as an alternative to cystectomy,[16–20,22] however, two studies enrolled patients unsuitable for surgery only [21,23].

There was some variation in the regimens used. Gemcitabine administration was based on a weekly schedule in five studies [16,18–21] and on a twice a week schedule in three studies [17,22,23]: concomitant cisplatin was planned in three studies [16,20,22]. Hypofractionated radiotherapy was given in 2 of the studies[18,19], contributing 32% of the patients analyzed. Radiotherapy was delivered to the bladder only in 5 studies [16–20]. while 3 studies (44% of patients) received nodal irradiation in addition [21–23].

The main features of the studies evaluated in this analysis are detailed in Supplementary materials (Table S1).

Patients' characteristics

One hundred and ninety patients were included in this analysis. The majority were males (87%), had an ECOG performance status 0 (76%), a T2 clinical stage (71%) and transitional cell carcinoma (TCC) only on histology (98%). The main patients' characteristics are shown in the Tables 1 and 2.

Clinical outcomes

Median duration of follow up was 44.5 months.

A post-treatment (usually within twelve weeks after treatment completion) cystoscopic re-evaluation was performed in 178 patients (94%). In these patients, a complete response was observed in 93% of the cases (166 patients). Among the 12 patients