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Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours

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ARTICLE INFO

Article history:
Received 21 July 2005
Accepted 12 August 2005
Available online 5 December 2005

Keywords:
Transitional cell carcinoma
Bladder cancer
M-VAC chemotherapy
Randomized trial
EORTC

ABSTRACT

EORTC protocol 30924 is an international randomized trial reporting a 7.3 year update of a 2 weekly regimen of high-dose intensity chemotherapy with M-VAC plus granulocyte colony stimulating factor (HD-M-VAC) compared to classic M-VAC in advanced transitional cell carcinoma (TCC). Two hundred and sixty three untreated patients with bidimensionally measurable TCC were included. In an intention to treat (ITT) analysis, there were 28 complete responses (CR) (21%) and 55 partial responses (PR) (41%), for an overall response rate (RR) of 64% on the HD-M-VAC arm. On M-VAC, there were 12 CR (9%) and 53 PR (41%), for an overall RR of 50% .The *P*-value for the difference in CR was 0.009; and for RR, was 0.06. After a median follow-up of 7.3 years, 24.6% are alive on the HD-M-VAC arm vs. 13.2% on the M-VAC arm. Median progression-free survival was better with HD-MVAC (9.5 months) vs. M-VAC (8.1 months). The mortality hazard ratio (HR) was 0.76. The 2-year survival rate for HD-M-VAC was 36.7% vs. 26.2% for M-VAC. At 5 years, the survival rate was 21.8% in the HD-M-VAC vs. 13.5%. Median survival was 15.1 months on HD-MVAC and 14.9 months on M-VAC. There was one death from toxicity in each arm; and more patients died to malignant disease in the M-VAC arm (76%) than in the HD-M-VAC arm (64.9%). With longer follow-up initial results have been confirmed, and shows that HD-M-VAC produces a borderline statistically significant relative reduction in the risk of progression and death compared to M-VAC.

1. Introduction

In Europe, cancer of the bladder is the fourth most frequent cancer among men [1]. Systemic chemotherapy is the only modality that has been shown in phase III trials to improve survival in responding patients with advanced bladder cancer [2,3] The M-VAC (methotrexate, vinblatine, adriamycin and cisplatin) regimen, first reported in 1985 at Memorial Sloan Kettering Cancer Center (MSKCC), revealed that urothelial carcinoma was sensitive to chemotherapy [4]. Patients with measurable lesions were found to have a 72% response rate (RR) and 36% attained a complete response (CR) [5]. Long-term survival was achieved in patients who attained CR. Overall survival for the entire population was 13.1 months.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.08.032

Chemotherapy was more effective in patients with nodal disease than in those with visceral metastases [3,5].

In an update of 5 different M-VAC regimens from MSKCC 194/203 patients were evaluable; 46 patients achieved CR (24%) and 84 patients PR (43%), with overall RR of 67%. The median survival for all 203 patients was 14.8 months, with a 5-year survival rate of 17% [6]. The 5-year survival for 46 CR patients after chemotherapy alone was 40%. An additional 30 patients achieved CR after chemotherapy was followed by surgery with a 5-year survival rate of 33% [7].

Prognostic factors were predictive of response and survival in these patients. Three risk categories on the basis of Karnofsky performance status (KPS) and the presence or absence of visceral metastases. Two factors had independent prognostic value: KPS less than 80%; and visceral (lung, liver, or bone) metastasis. Median survival times for patients who had 0, 1, or 2 risk factors were 33, 13.4, and 9.3 months, respectively ($P = 0.0001$). The median survival time of patient cohorts could vary from 9 to 26 months simply by altering the proportion of patients from different risk categories [6].

In an attempt to improve upon the results obtained with M-VAC chemotherapy, the present trial was initiated as a randomized phase II trial in June 1993 evaluating toxicity and activity and became a randomized phase III trial from April 1996 until November 1998. European Organization for the Research and Treatment of Cancer (EORTC) Genitourinary Group members from institutions in 8 countries participated in this protocol. The 3.2 year median follow-up results were first reported at ASCO in 2000 and published in 2001 [8]. The primary objective was to demonstrate an improvement in survival with HD-M-VAC. The current report seeks to update our experience with a median follow-up in both groups of 7.3 years.

2. Patients and methods

Patients with bidimensionally measurable distant metastases or unresectable TCC of the urinary tract (bladder, ureter, or renal pelvis) with no prior systemic cytotoxic or biologic treatment, and a WHO performance status of 0 or 1 were eligible for this trial. Patients were randomized 1:1 between HD-M-VAC which consisted of Methotrexate (MTX) 30 mg/m^2 d 1,Vinblastine (VBL) 3 mg/m^2 d 2, Adriamycin (ADM) 30 mg/m^2 d 2 and Cisplatin (CDDP) 70 mg/m^2 d 2 with Granulocyte Colony Stimulating Factor (G-CSF) administered on days 3–7 every 15 days vs. M-VAC (MTX 30 mg/m^2 d 1;VBL: 3 mg/m^2 d 2; ADM: 30 mg/m^2 d 2; and CDDP 70 mg/m^2 d 2 with MTX and VLB on d 15 and 22) every 28 days (Fig. 1).

Stratification was according to the treating institution and WHO performance status. The main endpoint of the phase III trial was overall survival. Secondary endpoints included progression-free survival, time to progression, response rate and toxicity. The objective of the trial was to detect a relative difference of 50% in median overall survival between the two arms from 12 months to 18 months (hazard ratio = 0.67). This corresponds to an absolute difference of 13% at the time of the median. With a two-sided logrank test at the 5% significance level and 80% power this objective required 192 events (deaths).

All analyses were carried out according to the intent-to-treat principle and statistical significance was claimed at the two-sided 0.05 level. Time to event comparisons were performed using the logrank test. Estimation of survival curves was by the Kaplan–Meier technique. Comparison of distribution of binary and non-ordered categorical variables was performed using the χ^2 test and that of continuous variables using the Wilcoxon Rank Sum test. Comparison of ordered categorical variables was performed using a χ^2 test for linear trend.

The intended dose–intensity ratio can be found in Table 1. With HD-M-VAC the dose intensity of ADM and DDP is doubled, but only 70% of the MTX and VLB dose are given compared to M-VAC (Table 1).

3. Results

Patient characteristics were well balanced between the two groups and are described in Table 2. One hundred and thirty four patients were randomized to the HD-M-VAC arm and 129 patients to the M-VAC arm. The median WHO Performance Status was 1. 40% and 31% had visceral metastases; 60% and 69% did not have lung, liver or bone metastases; 20% and 15% had prior radiation therapy; and 73% and 75% had prior surgery, respectively, for HD-M-VAC and M-VAC arms.

Generally, the patients who participated in this trial were very ill, with widely distributed metastatic disease. Sites of disease were equally distributed between the two arms (Table 3). Only 1/3 of patients had only one measurable disease site; and approximately 2/3 had two or more disease sites. The majority of patients in both arms had abdominal masses (pelvic, extranodal, and retroperitoneal). There were more patients in the M-VAC arm with lung metastases (29% vs. 12%)

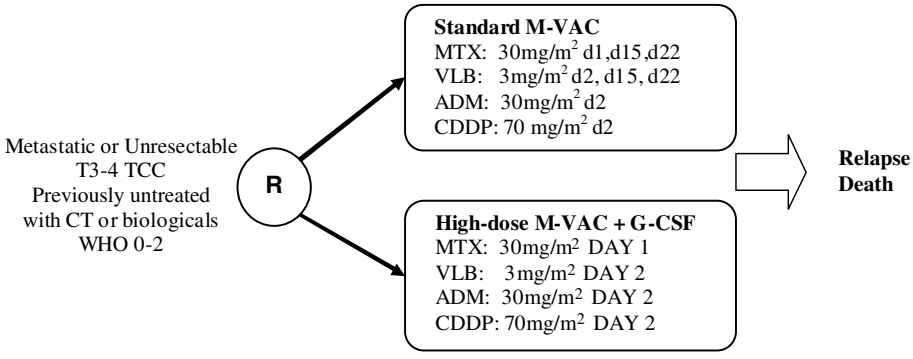

Fig. 1 – Trial design. Standard M-VAC is given every 28 days. High-dose M-VAC + G-CSF is given every 15 days.