Chemotherapy for bladder cancer. Fit, unfit and elderly: which treatment for which patient?

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Abstract

Cisplatin-containing combination chemotherapy has been the standard of care in the treatment of urothelial cancer (UC) since the late 1980s. However, up to 50% of patients are unfit for cisplatin-containing chemotherapy, either due to a poor PS and/or impaired renal function, or due to co-morbidity that forbids high-volume hydration. These conditions increase with age. The peak incidence of UC is in patients >60 years. In general, the absolute number of cancer cases in persons aged 65 years and older is expected to double between 2000 and 2030 and the proportion of those aged 75 years and older is projected to increase from 30% in 2000 to 42% in 2050. Therefore, we expect an increasing number of patients >65 years with UC in the near future.

So far, no standard chemotherapy has been established for patients ineligible for cisplatin-based standard chemotherapy.

Results: Trials with clearly defined 'unfit' patients or patients with multiple adverse prognostic factors are rare. The first randomised phase II/III trial in this setting was conducted by the EORTC and recently presented (De Santis et al, ASCO annual meeting 2010) and compared carboplatin/vinblastin/methotrexate (M-CAVI) and carboplatin/gemcitabine (GC) in patients unfit for cisplatin. Recently, the phase III data of this trial were presented and for the first time, overall survival (OS) and progression free survival (PFS) data for

this patient group was available. The ITT analysis (n=238) of the primary endpoint OS did not show a statistically significant difference between the two treatment arms with a median OS of 9.3 and 8.1 months (mos) for GC and M-CAVI, respectively. Median PFS was 5.8 mos on GC and 4.2 mos on M-CAVI. Both regimens were active with an overall response rate of 41.2% and 30.3% for GC and M-CAVI, respectively. For confirmed responses, the difference was statistically significant in favor of GC (p=0.01). Severe acute toxicity was higher on the M-CAVI arm (9.3% on GC and 21.2% on M-CAVI).

Conclusion: Patients ineligible for cisplatin benefit from carboplatin-based combination chemotherapy. GC was less toxic but about as effective as M-CAVI. New strategies for clinical studies in patients with impaired renal function, PS 2 and/or comorbidities should be designed and prioritized.

Introduction

The burden of cancer is increasingly shifting to the elderly and will have been doubled by 2050, mainly due to an increase in patients above 65 years[3]. Bladder cancer is a disease that mostly affects the elderly population. Issues that still need addressing include the impact of age in the treatment of advanced and/or metastatic urothelial cancer (UC) whether or not cisplatin is at all needed in the treatment of elderly and frail patients. The presentation will further discuss the criteria used to define who is "unfit" for cisplatin, and studies assessing the value of patient selection and individualised treatment.

Standard chemotherapy

The standard chemotherapy for advanced or metastatic urothelial cancer in 2010 is cisplatin - containing combination chemotherapy with gemcitabine/cisplatin, MVAC, preferably with GCSF, and HD-MVAC plus GCSF. This is level-one evidence and was rated as a grade A recommendation in the EAU guidelines and ESMO Clinical Practice Guidelines.

Long term follow-up of cisplatin combination-chemotherapy from randomized phase III-trials of the post-MVAC-era showed that there is long term survival (only) with cisplatin combination-chemotherapy. (slide 4)

The results with any of our therapies depend on prognostic factors. The most well known publication by Bajorin showed that KPS < 80 and visceral metastases were statistically significantly associated with poorer overall survival in an MVAC series from the MSKCC (Memorial Sloan Kettering Cancer Center). Depending on the number of poor risk factors the patients lived 9.3 mos if they had 2 and up to 33 mos if they had none of these two risk factors. (slide 5).

Treatment of bladder cancer in the aging population

Cisplatin is one of the main challenges in treating bladder cancer in the aging population (slide 9), as it is associated with a number of potential problems and sides effects (slide 10). Treatment with cisplatin is time consuming, because it requires overnight hospitalisation or prolonged outpatient intravenous hydration. Furthermore, cisplatin therapy may lead to quality of life deterioration, and is associated with adverse drug reactions that include nausea, fatigue, fluid overload, cardiovascular risk, renal toxicity ototoxicty and neurotoxicity (slide 1011).

However, these are no ~~grounds~~ reasons ~~for discarding~~to withhold ~~the use of~~ cisplatin altogether, since cisplatin combination therapy has been shown to increase long-term survival, in particular in patients without visceral metastases[4] (slide 4). Cisplatin is superior to carboplatin in cisplatin-eligible patients, although this statement is not supported by level1 evidence, as there are no data from randomised phase III studies. A study comparing methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) *vs.* carboplatin plus paclitaxel was terminated early due to slow accrual[5]. Randomised

phase II studies are nevertheless available (Table 1) and have shown that the addition of carboplatin to methotrexate and vinblastine led to reduced complete response (CR) rates and decreased OS compared with M-VAC[6-8]. Phase II studies combining carboplatin and paclitaxel resulted in a low overall response rates (ORR), low CR rates, and lower OS values (8.5–9.5 months) compared with those obtained with gemcitabine plus cisplatin (GC) or M-VAC[9-11] (slide 12~~3~~).

Impact of age

Chronological age does not necessarily correlate with functional impairment, and physiological impairment varies substantially between individuals, a fact that should always be taken into account when administering therapy. The cut-off age to define “elderly” may thus appear arbitrary.

"Elderly" vs. "unfit": who are the "unfit"?

More than 50% of patients with urothelial cancer are not eligible or “unfit” for cisplatin-based chemotherapy. The reasons for this include comorbidities and an elevated PS. So far, no standard chemotherapy has been established for this patient group. Ineligibility for cisplatin is usually selected according to the degree of functional impairment, which includes renal function, comorbidities such as congestive heart failure, cardiovascular risk factors, neuropathy, or amblyacousia (slide 7). [14,23-25].

The EORTC definition made for the purpose of developing study strategies in patients who are "fit" and "unfit" for cisplatin, is as follows: "fit" patients have a GFR ≥60 ml/min and PS 0–1. On the other hand, "unfit” patients have a GFR <60 ml/min and/or a PS of 2. This EORTC strategy aimed to conduct the first randomised phase II/III trial in "unfit"

UC patients (slide 15). Therefore, the EORTC 30986 study assessed GC *vs.* M-CAVI in previously untreated patients who were "unfit" for cisplatin-based chemotherapy ~~(Table 2)~~[1,2].(slide 1~~4~~6).

The ORR and median OS efficacy values were 44% and 8 months, respectively[26]. Only patients ineligible (unfit) for cisplatin-based chemotherapy were included in the EORTC study 30986. The ORR was 42% on GCa and 30% on M-CAVI, which prompted the authors to continue with the phase III part of the trial[1,2,] that included 119 patients on each treatment arm (slide 17). Patient characteristics were balanced, apart from a slight imbalance in favour of the GCa arm for the presence of visceral metastases (slide 18). ~~.~~ Of note, the median age was 70 in the GCa group and 72 in the M-CAVI arm, which is ten years more than patients included in cisplatin-based chemotherapy trials (slide 17). In addition, about 50% of these patients were reported to have associated chronic diseases[1] (slide 17).

The most commonly reported toxicities were grade 3/4 leucopenia, neutropenia, thrombocytopenia, febrile neutropenia and infection. Severe acute toxicity, defined as death due to toxicity, grade 4 thrombocytopenia with bleeding, grade 3/4 renal toxicity, grade 3/4 neutropenic fever or grade 3/4 mucositis at least possibly related to study drug occurred in 9.3% of patients in the GCa arm *vs.* 21.2% patients in the M-CAVI arm ~~(Table 19)~~[1].

In terms of efficacy parameters, the best ORR (CR plus partial response) was similar to phase II data, with a 41.2% response on GCa and 30.3% in the M-CAVI arm ~~(Table 20)~~. The difference in ORR between the two treatment arms did not reach significance (p=0.08), but the difference in confirmed response rate between the two treatment arms

was statistically significant (p=0.01)[1] (slide 18). Progression-free survival (PFS) in this unfit population was disappointingly low, and no statistically significant difference was observed: 4.2 months (95% confidence interval [CI]: 3.7–5.9) with M-CAVI *vs.* 5.8 months with GCa (95% CI: 4.8–6.9), hazard ratio (HR) =1.04 (95% CI: 0.80–1.35), p=0.78 (slide 1921). At a median follow-up of 4.5 years, only 9 patients on GCa and 11 patientsa on M-CAVI were still alive. In terms of the OS primary endpoint, no difference was recorded: 8.1 months with M-CAVI (95% CI: 6.1–10.3) *vs.* 9.3 months with GCa (95% CI: 7.6–11.3), HR=0.94 (95% CI: 0.72–1.22), p=0.6[1] (slide 213).

Formatiert: Nicht Hochgestellt/ Tiefgestellt

Survival data of study subgroups showed interesting results: both study treatment arms were grouped, and the patients were divided according to stratification factors (pre-planned) or Bajorin risk groups (*post-hoc).* When patients had only one reason to be unfit for cisplatin, or fewer Bajorin risk factors, survival was significantly better (slide 224). The study assessed patients in the subgroups with PS 2 and GFR <60 ml/min or those in Bajorin risk group 2. These patients had a rather adverse outcome, with an OS of only 5.5 months and response rates of 26% and 20%, respectively. In addition, SAT rates were high (26% and 24%, respectively). These patients had a 20% chance of receiving only one chemotherapy cycle (slide 235). Therefore, most patients in these subgroups did not benefit from this combination chemotherapy, and there may have been better outcomes with monochemotherapy regimens (for instance with gemcitabine), a special clinical trial setting with novel agents, or even with best supportive care[1,2].

How to better select patients for chemotherapy?

There are several points of interest for better selecting UC patients for chemotherapy: Performance status is important, but functional status in elderly (>75) may be more important, although there are not enough available data to support this[14,23-25]. Comorbidity is the rule and not the exception in elderly UC patients, but the rating of comorbidity by e.g. Charlson score has not became a standard so far. Renal function assessment is a challenge in elderly patients. Renal function assessment in the elderly can be less straightforward than expected. It is common knowledge that calculated creatinine clearance (CrCl) with current formulas tends to under-estimate CrCl in patients >65 years compared with measured CrCl. Thus, an evaluation of CrCl by simply using the calculating method might exclude patients who can tolerate cisplatin[13,14] (slide 2~~6~~4)

Future data

There are a number of ongoing trials and pending results in the first-line treatment of unfit or elderly urothelial cancer patients (slide 2~~7~~5). A first-line randomised phase II trial with vinflunine and gemcitabine *vs.* vinflunine and carboplatin is planned. The best regimen from this trial will be further evaluated in a phase III study (slide 2~~8~~6).

Conclusions

In conclusion, comorbidity is the rule and not the exception in elderly UC patients. The management of urothelial cancer in "unfit" patients ineligible for cisplatin-based chemotherapy concerns up to 50% of patients. The EORTC has defined "unfit" as patients with PS 2 and/or GFR <60 ml/min. In these patients, M-CAVI and GCa are active in the first-line setting, but they have different toxicity profiles, including more SAT

with M-CAVI. Patients ineligible for cisplatin are not a uniform group (slide 30): in patients with PS≥2, and GFR <60 ml/min or two Bajorin poor prognostic factors, little benefit from combination chemotherapy has been observed (slides 279, 2931). We are still in need of better patient selection criteria, better treatment options for patients with comorbidities and more clinical trial options for “unfit” patients and subgroups (slide 3032)

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