irreversible because of permanent cardiac damage and are associated with poor prognosis.[10]

Our analysis has some limitations that should also be taken into consideration. We did not discriminate between asymptomatic cardiac dysfunction, which might not be clinically relevant, and other toxic effects such as significantly reduced left ventricular ejection fraction and congestive heart failure. Finally, one of the studies included was not randomised,[7] which might bias our results.

To validate this treatment approach in the clinical setting, a properly powered, randomised phase 3 clinical trial is needed. Such a trial should consider sequential versus concomitant administration of trastuzumab and anthracycline-based chemotherapy. In previous large randomised phase 3 studies, which used the sequential approach in nearly 10 000 patients, a 50% reduction in the risk of relapse at the expense of a risk of congestive heart failure of up to 4% was deemed an acceptable risk–benefit ratio.[3,4] To put this outcome into perspective, a new strategy that entails the combined use of anthracyclines and trastuzumab should achieve a higher risk–benefit ratio (ie, increased benefit without compromising the risk). Until this result is convincingly shown, we strongly discourage the concurrent use of trastuzumab and anthracyclines-based regimens in clinical practice outside of the context of a clinical trial.

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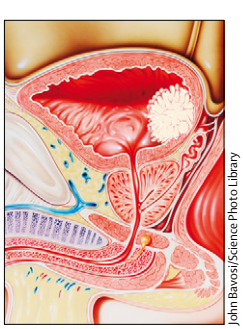
A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy

Worldwide, more than 386 000 patients are diagnosed with urothelial carcinoma (UC) every year, and more than 150 000 will succumb to the disease.[1] Although from 2003–07, the median age at time of death from UC was 78 years,[2] in the past few decades, the median age for patients enrolled in phase 3 trials that assess cisplatin-based chemotherapy regimens for metastatic UC has been 64 years.[3] This discrepancy, and the associated high rate of renal insufficiency and impaired functional status with advancing age,[4] has resulted in a disconnect between treatment efficacy and treatment effectiveness when applied to the general population of patients with UC. Investigators have long appreciated this disconnect, and have designed trials specifically for patients who are unfit for cisplatin-based chemotherapy;[5] however, variability in the eligibility criteria defining unfit patients has created difficulty in interpretation of the results. A clear and consistent definition is needed of enrolment criteria for future trials of patients with metastatic UC who are unfit for cisplatin-based therapy.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In 1997, the European Organisation for Research and Treatment of Cancer (EORTC) did a survey[6]

of 40 genitourinary medical oncologists to define cisplatin ineligibility. The survey defined preserved renal function (ie, creatinine clearance of greater than or equal to 1 mL/s) and a WHO performance status of 0 or 1 as prerequisites for cisplatin-based chemotherapy. Many clinical trials have subsequently been done in the unfit population, and have used heterogeneous eligibility criteria including creatinine clearance less than 1 mL/s, a WHO performance status of 2, old age (>75 years), a solitary kidney, poor functional status, or comorbidities.[5]

To try and develop a consensus definition for patients with metastatic UC who are unfit for cisplatin-based chemotherapy (panel), we assembled a working group of genitourinary medical oncologists and developed the following approach. First, we surveyed 120 international medical oncologists who were involved in clinical research of UC. Subsequently, we reviewed the available published work of ineligibility to cisplatin in UC and in other solid tumours. Finally, we reconciled the survey results and findings from the published works to generate a consensus definition. In view of the direct relation between age and creatinine clearance, data for the use of advanced age alone as a contraindication for cisplatin-based therapy are difficult to interpret. Age was not a prognostic factor for survival in patients with advanced UC who had been treated with cisplatin-based chemotherapy.[7] Thus, the available data—and the consensus from our survey—suggest that age alone should not be used as an eligibility criterion for clinical trials of unfit patients.

Renal mass and renal blood flow decrease with age, resulting in a gradual loss of functioning nephrons. Beyond the ages of 30–40 years, renal function declines by about 1% every year, such that renal function has declined by about 40% at the median age of diagnosis of advanced bladder cancer. The effect of age, together with urinary-tract obstruction related to bladder cancer, and smoking-related vascular disease, leads to a very high rate of renal impairment in patients with UC.[4] Although the optimum method to measure renal function that balances cost, convenience, and accuracy, has been debated, the International Society for Geriatric Oncology Task Force on Renal Safety in the Elderly recommends use of the Cockroft-Gault equation for calculating creatinine clearance (except for elderly patients with chronic renal insufficiency, for whom the Modification of Diet in Renal Disease equation might be preferred).[8]

Because cisplatin is cleared by the kidneys, potentially nephrotoxic and pre-existing renal impairment is a risk factor for nephrotoxic effects. Cisplatin is routinely avoided in patients with renal impairment. Although there are no definitive studies to help guide the threshold level of renal function that should preclude cisplatin, a review of cisplatin-based chemotherapy trials that are listed on ClinicalTrials.gov confirms the standard threshold of a creatinine clearance of more than or equal to 1 mL/s as the most commonly used inclusion criterion. This threshold was the most commonly selected by our survey respondents, and is appropriate for defining patients who are unfit for clinical trials. Cisplatin use in patients with a solitary kidney has been controversial, and is perhaps most germane to patients with metastatic upper-tract UC who have undergone nephroureterectomy. A study assessed the renal safety of cisplatin-based chemotherapy in 60 patients with metastatic UC and a solitary kidney, and noted a significant decline in estimated glomerular filtration rate after three cycles of treatment.[9] However, this decline correlated with baseline renal insufficiency and led to clinically significant renal toxic effects in only three patients. Therefore, with no impaired renal function, patients with a solitary kidney need not be uniformly considered as cisplatin-ineligible—a conclusion that is also favoured by the results of our survey. Clearly, extra care with vigorous hydration is warranted in this setting to optimally preserve renal function.

Poor functional status has been associated with increased toxic effects and decreased efficacy in patients with metastatic UC who are treated with cisplatin-based chemotherapy.[7] Our survey respondents most commonly selected an Eastern Cooperative Oncology Group (ECOG) performance status of more than 2 as an

***Panel*: Consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy**

Patients meeting at least one of the following are considered "unfit"

- WHO or ECOG performance status of 2, or Karnofsky performance status of 60–70%
- Creatinine clearance (calculated or measured) less than 1 mL/s
- CTCAE version 4, grade 2 or above audiometric hearing loss
- CTCAE version 4, grade 2 or above peripheral neuropathy
- NYHA class III heart failure

ECOG=Eastern Cooperative Oncology Group. CTCAE=Common Terminology Criteria for Adverse Events. NYHA=New York Heart Association.

inclusion criterion for unfit patients. However, only one trial in this population has included patients with an ECOG performance status of 3 and the safety of cytotoxic therapy in this population is not well characterised. Therefore, in the absence of further prospective studies showing the safety of chemotherapy in patients with advanced UC and a performance status of 3, the working group favours an ECOG performance status of 2 as an eligibility criterion for clinical trials of unfit patients. Similarly, the relation between comorbidities, treatment efficacy, and treatment-related toxic effects is complex and has not been adequately explored in patients with advanced UC. Congestive heart failure was selected by many of the survey respondents, and New York Heart Association class III–IV heart failure is often an exclusion criterion for cisplatin-based trials.

The use of cisplatin is limited by nephrotoxic, neurotoxic, and ototoxic effects. Although there is substantial variability in the susceptibility to hearing loss due to cisplatin, risk factors include renal impairment, older age, and pre-existing hearing loss. Hearing loss after cisplatin occurs mainly at high frequencies and at cisplatin dosages greater than 60 mg/m^2.[10] The Common Terminology Criteria for Adverse Events version 4 (CTCAE) defines grade 2 auditory loss as decibel losses of 25 dB at two contiguous frequencies. Because cisplatin can induce hearing loss of 19–20 dB, the use of cisplatin in patients with pre-existing hearing loss is likely to induce additional damage, potentially resulting in hearing loss of grade 3 or 4. Therefore, the working group favours baseline audiometric hearing loss that is equal to and greater than grade 2 to define the unfit population.

The risk of cisplatin-induced peripheral neuropathy is increased in patients with pre-existing neuropathy, and about a fifth of survey respondents selected this symptom for defining unfit patients. In view of the effect of severe neuropathy on ambulation and quality of life, the working group recommends inclusion of a CTCAE grade 2 and above peripheral neuropathy to define unfit patients. The use of these concise criteria to define unfit patients with metastatic UC will lead to more uniform clinical trials, enhanced ability to interpret trial results, and a greater likelihood of developing a viable strategy for regulatory approval for treatment of this important subset of patients. Notably, these criteria are not meant to replace clinical judgment for selection of patients for cisplatin-based therapy who are not being treated in the setting of a clinical trial, because the risks and benefits of proceeding with cisplatin might be influenced by the ultimate goals of treatment (eg, palliative *vs* curative intent). Ideally, new agents with improved efficacy and tolerability will eliminate the need to assess patients with metastatic UC in these separate cohorts in the future.

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For a list of those who participated in our survey see webappendix.

See **Online** for webappendix

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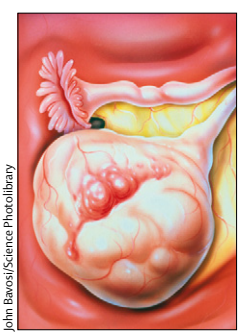
New terminology for cytoreduction in advanced ovarian cancer



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The goal of primary cytoreductive surgery for the treatment of advanced ovarian cancer (FIGO stages II–IV) should be to achieve a reduction to microscopic disease, as cytoreduction to nodules of less than 1 cm in maximum diameter is associated with a clear benefit in terms of overall survival compared with patients who have larger residual disease.[1]

During the past 30 years the meaning of the term optimal cytoreduction in advanced ovarian cancer has been used variously. Hacker and co-workers,[2] used this terminology for patients with a largest residual tumour mass of 1·5 cm or less in diameter; they described a median survival of 6 months for residual tumours larger than 1·5 cm, 18 months for those with tumours 0·5 cm to 1·5 cm, and 40 months for patients with a tumour mass of less than 0·5 cm. Subsequently, Hoskins and colleagues[3] defined optimal as a residual tumour of 2 cm or less in diameter, but the patient cohort with microscopic residual disease they studied had a better prognosis than usual. Bristow and colleagues[4] used a definition of residual disease of 1 cm or less in patients with stage IV ovarian cancer, and reported a significant median survival difference (p=0·0004) between the two groups using this cutoff (38·4 months *vs* 10·3 months). By contrast, others[5] have used the term optimal cytoreduction when removal of all evidence of macroscopic disease is achieved. Chi and colleagues assessed 465 patients with advanced ovarian cancer who underwent primary cytoreductive surgery and noted significant overall survival differences (p<0·01) between patients with no gross residual disease, gross residual disease of 1 cm or less, and gross residual disease greater than 1 cm.

The variable definitions used for the terms optimal and suboptimal after cytoreductive surgery for ovarian cancer makes comparisons of previous studies difficult. Therefore we regard this nomenclature to be suboptimal and its use should be avoided. Since most referral centres do not achieve complete removal of macroscopic disease after cytoreductive surgery in more than 30% of patients with ovarian cancer,[1] the definition of cytoreduction should include three prognostic groups which are relevant in terms of survival (no macroscopic disease, macroscopic disease up to 1 cm, and macroscopic disease larger than 1 cm). The three groups could be referred to as complete resection, minimal residual, and gross residual, respectively. In this way, by establishing a uniform terminology that links to patient prognosis, we might provide accurate information to our patients.

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