adverse events [2]. Hemorrhagic cystitis in patients previously subjected to pelvic radiation therapy was named as radiation recall syndrome induced by CBZ [3]. In previous case series, differential diagnosis of hematuria induced by disease progression was eliminated by TURB. In our patient, this adverse event was an unexpected reaction to CBZ. The mechanism of this reaction to CBZ is not known as yet. Seventeen percent hematuria of all grades was found in the CBZ arm of the TROPIC, and the metabolism of CBZ, which occurs mainly in the liver, does not provide an explanation for the occurrence of hemorrhagic cystitis [4]. During gross hematuria, he had no coagulation disorder or liver dysfunction. Adverse reaction report was performed by the manufacturer to the Pharmaceuticals and Medical Devices Agency in Japan.

Our case may guide management of patients with gross hematuria after the treatments with CBZ and suggests the importance of urological investigation with drug withdrawal.

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Disclosure

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References


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Era-by-era improvement in survival for elderly patients with Hodgkin lymphoma; outcome data from a large population-based cohort

Hodgkin lymphoma has cure rates of 70%–95% for younger patients; however, outcomes for older patients remain significantly worse [1, 2]. Possible explanations include greater co-morbidity, inferior outcome following relapse, and increased unrelated deaths. Moreover, ‘fit’ older patients traditionally enrol on to studies for younger patients, with greater toxicity, while those with co-morbidities are poorly represented in studies [1].

The Nottinghamshire Lymphoma Registry contains details of all patients diagnosed with lymphoma within Nottingham University Hospitals and Sherwood Forest NHS Trusts since 1973. Our group previously described improvements in survival for Hodgkin lymphoma in all ages from 1973 to 2002. The present study focused exclusively on patients aged 60 years and over, extending the analysis to 2012.

Treatment details for patients diagnosed 1973–2003 have previously been described [3]. From 2003 to 2012, ChlVPP–PABIOE remained the preferred regimen, with ABVD used in highly selected patients, while frail patients were typically treated with ChlVPP alone.

The primary outcome was survival, and Cox regression analysis was used to compare survival over the eras. Two hundred and eight patients aged 60 years and over were identified. The median overall survival was 2.44 years, ranging from 0.49 years for 1973–1977 to 6.42 years for 2008–2012. Marked improvement was seen after 1998, with median overall survival from this time-point over 6 years (Figure 1). The median age within different eras was not the explanation, as there was a trend towards increased age in the later eras.

By univariate analysis, era of diagnosis was highly predictive of survival (P = 0.0017). Age (P = 0.0002) and male sex (P = 0.024) also predicted outcome. Applying multivariate analyses, each variable continued to be significant. Analysing for trend suggested era of diagnosis to be the most important determinant of outcome (P < 0.001). There were no statistical interactions between age, sex and era in determining outcome; thus, no sub-group of patients failed to benefit from the improvement in survival over time.

Our population-based data demonstrates, in contrast to published reports [4], marked era-by-era improvements in survival for older patients with Hodgkin lymphoma. It is unlikely that type of chemotherapy regimen accounts for improvements seen from 1998, as similar treatments were employed from 1993 to 2012. Patients after 1998 likely benefitted from improved supportive care, routine use of G-CSF and neutropenic prophylaxis, improved health, and physician inclination to treat aggressively. Lack of improvement in the most recent era suggests the limit of conventional chemotherapy and supportive care may have been reached. An absence of co-morbidity data limits our study, as we cannot delineate ‘fit’ and ‘unfit’ elderly patients. Current prospective studies are
attempting to address this with formalised co-morbidity scoring. Notwithstanding this, our population-based cohort provides 'real world' outcomes demonstrating improvements in survival for patients under-represented in clinical trials.

Outcomes from our population-based study of older patients diagnosed 1997–2012 appear comparable with recent phase II studies of selected ‘fit’ patients [2, 5]. These single-arm studies again may reflect improved patient health and willingness to treat aggressively, rather than improved chemotherapy regimens. Well-conducted clinical studies for ‘fit’ and ‘unfit’ older patients are required to better understand outcomes in the modern era.

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The ESMO magnitude of clinical benefit scaling tool: from theory to practice

The article by Cherny et al. in this journal presenting the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) provides a very relevant contribution to the discussions how to assess new available cancer therapies in terms of their innovative add-on, clinical benefit and value for patients [1]. The ESMO-MCBS is advancing the critical public policy debate of value in cancer care.

Providing a standardised template for grading clinical benefit, the scaling tool facilitates semi-quantitative clinical benefit assessments. Caution has been taken by the ESMO task force to validate the MCBS through field testing involving more than 300 oncologists and expert statisticians plus subsequent applications of the scale to contemporary and historical controlled clinical trials.

Similarly, by their case-by-case approval decisions, the European Medicines Agency (EMA) has set over many years thresholds for efficacy judgements [2]. The Agency itself is moving forward to a quantitative approach for benefit–risk (BR) evaluations [3], and is in the process to tackle the so-called fourth hurdle of effectiveness through joint evaluations with the national authorities which are responsible for health technology assessment (HTA) and pricing and reimbursement decisions [4]. The nationally acting authorities are attempting, under the roof of the European network for HTA (EUnetHTA), to effectuate more reliable and stringent processes for the relative effectiveness assessments of new therapeutic modalities [5].

In contrast to the regulatory decision-making process—all approvals of new cancer drug are granted since 2006 EU-wide by the EMA—the pace of European integration in terms of HTA and pricing and reimbursement decisions is however delayed resulting in the well-documented lack of equal access to cancer drugs across the EU [6]. Decisions are taken nationally with sometimes limited transparency, and the assessment methodology is still in the stage of refinement. Currently decision patterns just start to emerge, as demonstrated exemplarily by the analysis of early benefit assessments (EBA) done by the German G-BA (Figure 1).

The continuance of the predominantly national HTA policy decisions, often driven by more or less recognisable cost-containment objectives, bears undoubtedly a risk to impede the objective of EU citizens’ rapid and equal access to high-quality medical care. In face of a passionate public debate on the costs and value of novel cancer therapies, the MCBS endeavor can succeed only, if ESMO’s dialogue with the national public policy makers is continued and intensified.

From theory to practice: the ESMO-MCBS may deliver its true significance, if the hitherto undertaken tool validation is pursued by comparisons with outcomes of national HTA decision-making, notably from those EU member states with relevant demographic weight. Gaining external validity would not only help to improve the accuracy of the MCBS, but should allow ESMO to assess in a watchdog-like manner whether and to what extent the actual HTA and value-decision-making across different EU countries and policy makers is well-balanced between access to innovation and pricing efficacy on one hand and adequate resource allocation and cost-containment on the other.