**Abstract 178 words**

**Introduction:**

The treatment of poor prognosis chemotherapy naïve or relapsed testicular cancer is challenging. In poor prognosis treatment naïve disease the outlook for patients with standard approaches utilising three weekly cisplatin based regimens, most commonly Bleomycin, Etoposide and Cisplatin (BEP) is suboptimal, and one can expect more than half of patients to relapse or progress and need salvage treatment. Recent randomised studies have lent weight to the use of dose intensified treatments in these selected patient groups. In relapsed testicular cancer post platinum based chemotherapy controversy exists as to the optimum relapse regimen, as significant cure rates can be expected by re-treating with both conventional dose and high dose or dose intense regimens.

**Areas Covered:**

This review seeks to outline the evidence for alternative approaches beyond standard three weekly cisplatin based regimens in poor risk metastatic disease. It also explores the evidence available for selection between conventional dose and high dose strategies on relapse.

**Expert opinion:** An overview of the data is presented to support personalising therapy selection in both poor risk and relapsed metastatic germ cell tumours.

## 1) Introduction

Testicular cancer is the most common cancer to affect men in their 3rd and 4th decade of life, and is largely curable even when metastatic. Since the advent of combination chemotherapy with cisplatin, bleomycin and vinblastine in the 1970's the cure rate for this disease in young men went from 5-10% to over 70%[1]. Further advances enabled the reduction in the duration of treatment from 2 years to 12 weeks, with no change in the overall cure rate[2]. Subsequently the substitution of vinblastine for a more effective and less toxic drug etoposide and the shortening of treatment for most patients to nine rather than twelve weeks

was achieved[3].  The paradigm of combination chemotherapy with BEP for the majority of patients with metastatic GCT who fall into the IGCCCG good or intermediate risk profile has not been bettered in a randomised study.

The IGCCCG prognostic grouping criteria for men with testicular cancer have been used as a validated benchmark, initially described in over 5000 patients with metastatic disease[4]. **Approximately 15% of patients present with poor-risk disease, either by virtue of the presence of non-pulmonary visceral metastases or high tumour markers. This group of patients have a cure rate of approximately 48% with 4 cycles of 21 day BEP chemotherapy. This compares to those in the good risk criteria which have a cure rate of over 90% with 3 cycles of BEP[5]. It is important to note that compared to these historic outcomes both poor and good risk patient outcomes are improved when treated with similar regimens in expert centres according to recent data, although a significant disparity still exists between the two populations of patients[6].**

It has long been recognised therefore that in the group of patients with poor risk NSGCT a different approach may be needed.  Although 4 cycles of BEP remains the standard approach that is espoused in both the European guidelines and the US guidelines, many expert clinicians feel that this is a suboptimal approach, and condemns the majority of patients to salvage therapy to achieve cure.   The following review will attempt to address the current literature surrounding this area, and to address this issue in second line therapy.

**2) The treatment of poor risk NSGCT, the case for dose intensity.**

Delivering a similar dose of chemotherapy over an accelerated timeframe is not a new concept in cancer treatment.  **The pioneering biostatistical work of Norton and Simon generated the concept of the "log kill" effect of cytotoxics, particularly well illustrated in the treatment of leukaemias with constant and rapid growth rates.  However this alone seemed less adept at explaining the cell kill rate seen in solid tumours, given that they are complicated by**

**Gompertzian growth curve plateaus[7]. The concept that greater tumour cell kill could be expected if cytotoxics were delivered over as short a time as possible gave birth to dose "dense" approached in solid tumours. As has been trialled in other cancers such as Non- Hodgkin lymphoma and breast cancer, this approach has also been applied in poor risk germ cell tumour treatment.** The literature is composed of mostly single centre phase 2 studies from large volume centres with only two randomised phase III clinical studies have compared BEP with dose intensified approaches. In early randomised studies it was established that doubling the cisplatin dose alone was not beneficial in terms of outcome, but did increase toxicity[8].  In 2007 the Sloan Kettering group reported a phase III study randomising 219 patients with intermediate or poor risk NSGCT to BEP x4 or BEP x2 plus tandem HDCT with carboplatin.  The durable complete response (CR) rate at 1 year was 52 % In the HD arm vs 48% in the BEP Arm, with no significant difference in survival across the cohort.  However this study did retrospectively identify a subgroup of patients (n=67) with poor marker decline after the first cycle of chemotherapy in whom the durable CR rate was 61% with dose intense therapy vs 34% with BEP[9].  In 2014 the GETUG-13 study was published further exploring the utility of tumour marker decline in defining a prognostic group in poor risk patients in whom to target dose intensification.  In this randomised study conducted in 20 centres tumour marker measurement at D18-21 post cycle one BEP determined randomisation into a dose intense arm including oxaliplatin, paclitaxel and ifosfamide.  263 patients were involved and 80% of these were determined to have an unfavourable marker decline at the end of cycle 1. The patients in this group who were randomised to the dose dense therapy had a three year progression free survival of 59% vs 48% in the standard BEP arm.  There was greater toxicity (largely haematologic) in the dose dense arm but no increase in on treatment toxic deaths[10].  The mature 5 year results from GETUG 13 show a PFS of 60% in the dose intense arm vs 47 % in the BEP arm **(HR: 0.65; p=0.037) with an OS of 78 % vs 61% (p=0.02)**[11].

Dose intense regimens have been pioneered in many UK centres. A Randomised MRC/EORTC study of early sequential BEP/EP vs intensified BOP/VIP-B showed no difference in the failure free overall survival between the two arms[12].  It has

been postulated that the lack of early exposure to etoposide in the dose intensified arm may have hampered efficacy in this study. Certainly investigators in good risk metastatic NSGCT have demonstrated that the 500mg/m2 dose is superior to 360mg/m2 [13]. Other regimens increasing density of exposure of platinum and retaining etoposide include the two weekly alternating POMB-ACE regimen introduced by investigators at Charing Cross Hospital[14] incorporating methotrexate at 500mg/m2 in addition to dactinomycin and cyclophosphamide which demonstrated an overall survival in poor risk NSGCT of 75% at three years including in patients with mediastinal primary tumours. Incorporating the POMB-ACE regimen but adding agents such as doxorubicin, a 2002 phase II study of the dose intensified BOP/CISCA POMB ACE regimen found a three year overall survival rate of 73% but a treatment related death rate of 7% [15].

St Bartholomew's Hospital introduced the GAMEC regimen incorporating higher doses of methotrexate (up to 8g/m2 ) together with early exposure to Etoposide at 500mg/m2 , cisplatin weekly, Dactinomycin and GCSF support[16]. In a phase II study including 27 treatment naïve patients in the poor risk group, progression free survival to GAMEC plus appropriate surgery was 74%. A further analysis of this regimen in 73 patients with poor risk untreated GCT has shown a 2 year PFS rate of 69% and a 3 year overall survival rate of 76.6%[17].

Interestingly long term outcome data from the GETUG-13 trial presented has shown potentially higher failure rates in the central nervous system on the dose intense therapy arm compared to BEP (approximately half of all relapses were in the brain) than may be expected[18]. **Of patients presenting with CNS disease the progression rates in the CNS at 1 year were 58%.** In the Bokemeyer analysis of GCT, brain metastases at presentation confer a overall survival rate of 43% with standard approaches[19]. Interestingly a retrospective review of 17 patients with CNS disease at presentation treated with GAMEC including high dose methotrexate showed a progression free survival of 71%, without the use of CNS irradiation[20]. **Recent data in press in patients with CNS disease treated with GAMEC shows a progression rate at 2 years of only 18%[21]. Although the optimal treatment of CNS disease is still unclear, the inclusion of agents such**

as etoposide and methotrexate with good CNS penetration together with cisplatin may be important to obtaining good clearance of disease in the brain.

The Royal Marsden developed the CBOP/BEP regimen, based on the principle introduced by Wettlaufer et al, utilising carboplatin in addition to cisplatin[22]. In a multicentre study of 54 poor risk patients the relapse free survival was 83.2%. The subsequent randomised TE23 MRC study[23] compared CBOP/BEP to 4 cycles of BEP. The primary outcome measure was favourable response rate (FRR) and 89 patients were randomised in the study. At 1 year the FRR was 74 % with CBOP/BEP vs 61% with BEP. The 2 years overall survival was 67% vs 61% with BEP. As expected CBOP BEP was more toxic with 3 toxic deaths compared to 2 in the BEP arm.

Despite differences in the nature of the drugs utilised, all of these treatments incorporate a 2 weekly regimen of cisplatin based treatment with early exposure to a range of other cytotoxic agents in addition to etoposide. Although none has been proven superior to BEP in randomised phase III studies, Phase II (randomised in the case of CBOP BEP) have shown excellent PFS rates compared to 4 cycles of BEP.

Several phase II studies in poor-risk patients have been conducted outside of the UK. A multicentre, single-arm phase II trial in the United States used paclitaxel, ifosfamide and cisplatin (TIP) in the frontline setting for patients with intermediate and poor-risk disease, on the basis of its efficacy in relapsed germ cell tumours. The patients received four cycles of TIP (paclitaxel 240mg/m2 over 2 days, ifosfamide 6g/m2 over 5 days with mesna support, and cisplatin 100mg/m2 over 5 days) on a 3-weekly basis. Of the 40 patients in the poor-risk group, the 3-year PFS and overall survival were 63% and 87% respectively. The favourable response rate (FRR) in this group was 74% with a complete response rate of 68%. We note only 1/40 patients in this study had CNS disease at presentation. Grade 3-4 toxicities predominantly consisted of haematological or electrolyte abnormalities[24].

Ongoing randomised clinical trials in this area include the phase III TIP vs BEP study in intermediate and poor risk disease (https://clinicaltrials.gov/ct2/show/NCT01873326) and the accelerated BEP study in the UK and Australia https://clinicaltrials.gov/ct2/show/NCT02582697.

**Table 1: Studies of alternative dose intense regimens in poor-risk GCT patients**

| Reference | Number of patients | Phase | Treatment | OS (%) | PFS (%) | FRR(%) | Treatment related deaths |
|---|---|---|---|---|---|---|---|
| Fizazi K et al 2002 | 58 | II | BOP CISCA POMB ACE | 3-year OS: 73% | 3-year PFS: 71% | NA | 7% |
| Shamash et al 2005 | 62 | II | GAMEC | 3-year OS: 76.6% | 2 year PFS: 68.5% | NA | 6.8% |
| Huddart et al 2015 | 89 | II | CBOP/BEP | 2-year OS: 67% | NA | 74% | 3.3% |
| Feldman et al 2016 | 38 | II | TIP | 3-year OS: 87% | 3-year PFS: 63% | 74% | 0 |
| Fizazi 2014 | 263 (203 with poor marker decline) | III | BEP + Dose intense treatment (oxaliplatin, ifosfamide, paclitaxel) | 5-year OS: 78% | 5-year PFS: 60% | NA | 1% |

PFS; progression free survival, OS; overall survival; FRR, favourable response rates

## 2.1) Expert Commentary: Poor risk disease – BEP and beyond

The path of progress by virtue of which we are able to cure most men with metastatic testicular cancer is nothing short of remarkable. The major trials that have led to this point have been methodical, have learned from their predecessors, and have slowly and robustly formed an evidence base defining a solitary regimen – BEP – as being the standard of treatment for most men with this disease. In good and intermediate risk disease, not many would question that this remains the gold standard and most men can expect cure with this regimen. However, it is in the rarest group of patients with this disease – those with de novo poor risk disease, that BEP fails to cure more than half of men. One could argue that utilising 4 cycles BEP chemotherapy in poor risk patients condemns over 50% of patients who will not be cured with first line therapy to salvage treatment to achieve cure, and not all those undergoing salvage will survive. To achieve cure they are therefore at best receiving 4 further cycles of platinum based conventional dose chemotherapy or high dose chemotherapy in the second or subsequent lines. Only recently however has a phase III randomised trial (GETUG-13) shown that a dose intense regimen may be superior in this setting. The idea of curing more men upfront is surely appealing. Looking at those regimens trialled in the phase II setting – CBOP/BEP, POMB/ACE, GAMEC, TIP and the Paclitaxel-BEP-Oxaliplatin regimen from the GETUG-13 protocol described above the broad 2-3 year progression free survival rate lies between 65-70% - over 20% greater than could be expected with 4 cycles of BEP.

We therefore believe that there are some populations who may benefit from this approach despite the higher toxicity inherent in many of these regimens. In our institution we utilise a dose intense regimen in this setting and believe this may specifically benefit patients with CNS disease at presentation or extragonadal primaries that seem to do better than would be expected with BEP. Conversely patients who are deemed not of sufficient physiological reserve, because of

advanced age, comorbidity or poor organ function, should not be offered dose intense treatment. Indeed in the GAMEC regimen published cohorts those patients with high LDH's and age over 35 do less well[16]. The selection of patients is therefore crucial for this approach, which a clear discussion regarding the risks and benefits of the dose intense versus standard treatment options. With the advent of the recent randomised studies described above, the tide may be turning to enable clinicians to challenge the status quo that 4 cycles of BEP is acceptable treatment for all patients with poor risk metastatic testicular cancer.

## 3) Relapsed testicular cancer after standard cisplatin based chemotherapy.

Although testicular germ cell tumours are highly curable, up to 60% of patients in the intermediate and poor risk group will relapse and require further therapy. Relapses generally occur within the first two years of initial treatment[25].

Unlike most other solid tumours, further exposure to platinum based chemotherapy following failure of first line chemotherapy can still be curative. Salvage treatment options include conventional dose chemotherapy (CDCT) and high dose chemotherapy with autologous stem cell rescue (HDCT). Conventional wisdom is that relapsed testicular cancer should be exposed to platinum plus agents to which the tumour is naïve such as ifosfamide. CDCT options therefore include cisplatin, ifosfamide and paclitaxel (TIP)[26], etoposide, cisplatin and ifosfamide (VIP/PEI) and vinblastine, ifosfamide and cisplatin[27]. There have been no direct comparison between the different combinations, but objective response rates and survival rates are relatively similar between the different regimens. TIP consists of four cycles of Paclitaxel, Ifosfamide and Cisplatin administered 21 days apart, with a dose of paclitaxel of 250mg/m2 given over 24 hours on day 1, ifosfamide 1500mg/m2 with mesna support on days 2 to 5, and cisplatin 25mg/m2 administered on days 2 to 5. In the phase II trial with 46 patients, the 2-year progression free survival rate was 65%, with a durable CR rate of 63%[28]. Other agents with efficacy in the relapsed setting include oxalipatin and irinotecan[29], and a phase II study is currently recruiting utilising methotrexate,

oxaliplatin and paclitaxel (GAMMA regimen see http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/).

An alternative treatment is high dose chemotherapy (HDCT), pioneered by Indiana University[30]. The largest single-institution study evaluating HDCT in patients with relapsed testicular tumours was published recently[31]. . They conducted an analysis of 364 consecutive patients with GCT who progressed after cisplatin-based combination chemotherapy and were given HDCT. Patients who had platinum-sensitive disease received one or two cycles of standard-dose chemotherapy, most commonly VeIP, before proceeding to HDCT. Two courses of HDCT were planned for all patients, each consisting of carboplatin 700mg/m2 plus etoposide 750mg/m2. Stem-cell infusion was performed on day 0. After engraftment and end-organ recovery, the second cycle of HDCT was initiated.

The 2-year progression-free survival in this cohort was 60%, and the 2-year OS 66%. A significant majority of these patients received HDCT as second-line therapy (2-year PFS 63%), with a minority (16.7%) receiving it as third-line therapy with a 2-year PFS of 49%.

These numbers were comparable to a smaller Phase I/II study performed in Memorial Sloan Kettering, albeit using a slightly different regimen[32]. This group used paclitaxel and ifosfamide as induction chemotherapy followed by high-dose carboplatin and etoposide with PBSCT for three cycles (TI-CE regimen). The reported 5-year disease survival was 47% and OS was 52%.

The largest controversy in this area is the choice of CDCT vs HDCT as the first salvage treatment. Practices vary worldwide with some clinicians employing high-dose chemotherapy as initial salvage therapy, whereas others use HDCT only after failure of initial CDCT as 2nd line therapy.

To date, there has only been only one randomised controlled trial with 280 patients, IT-94, between HDCT and CDCT[33]. This trial displayed similar ORR (approximately 55%), event-free survival (35 vs 42%) and 3-year overall survival

between HDCT and CDCT (both 53%). There were more toxicities in the HDCT arm, and more toxicity-related deaths (7% vs 3%). However, the trial has been criticised for methodological issues. In particular, it only employed the use of one cycle of HDCT which is thought to be suboptimal compared to tandem cycles of high dose. It has also been criticised for a relatively small data set, and a predominance of low-risk patients.

A large retrospective study was performed in 2011 by Lorch et al[34], comparing CDCT vs HDCT in a group of 1435 patients. The hazard ratio for PFS was 0.44 stratified on prognostic category, and the hazard ratio for OS was 0.65, favouring HDCT. These results were consistent in all prognostic groups except the low-risk patients, where similar OS values were identified. As with all retrospective studies, caution has to be exercised in interpreting these results in the context of selection bias, particularly positive selection bias for HDCT. There were also a variety of different salvage chemotherapy regimens used for CDCT and HDCT contributing to heterogeneity in analysis. However despite these limitations this was the largest dataset compiled in this setting and strongly suggested that in patients, particularly those deemed high risk, HDCT outcomes were superior.

A large systematic review[35] attempted to address this issue with an analysis of 59 studies. In the pooled analysis, it found no significant differences in efficacy, whether comparing 1-year OS (64.2% in CDCT vs 63.7% in HDCT), 3-year OS (45.1% vs 46.7%) and 5-year OS (43% vs 45%). HDCT was predictably associated with a higher risk of mortality (1.29% in CDCT vs 6.46% for HDCT). **There have been no analyses of the differences in long-term toxicities between CDCT and HDCT, which is an important point to be studied in future trials. However, it is clear that patients who survive multiple lines of treatment are prone to long term side effects such as second cancers, major cardiovascular disease, pulmonary disease, and GI disease[36].**

An ongoing randomised phase 3 trial (TIGER) will provide an OS comparison between TIP and paclitaxel-ifosfamide followed by three cycles of high dose carboplatin-etoposide (TI-CE) in progressing/recurrent GCTs. The trial is

currently recruiting and aims to answer this key question in germ cell tumour management.

**3.1) Expert Commentary: The Optimal Choice of Salvage Treatment**

**Despite the celebrated success of cure rates in germ cell tumour, 20-30% of patients with metastatic cancer relapse and for them the prognosis can be variable but there is still a good chance of cure. There are multiple conventional dose regimens as well as the choice of high dose chemotherapy. Little progress in concluding which of these options are best has been made, but some retrospective data points towards superiority of the high dose approach, particularly in those patients at high risk of failure. One of the major difficulties in evaluating results of salvage treatment in large, but predominantly retrospective studies, is the heterogeneity of patients at this phase of the illness. The variable factors include extent of disease at presentation, the duration and degree of response to primary chemotherapy, residual organ tolerance (such as renal function), as well as the extent of disease at relapse.**

**Many clinicians employ the practical approach of using only CDCT in the favourable prognostic group, while reserving HDCT only for those with poor prognosis, using the criteria set out by the International Prognostic Factors Study Group. This approach is sensible insofar that high dose chemotherapy can be offered as third or further line therapy at the point of relapse. One of the main arguments against this approach would be the theoretical accumulation of long-term toxicities from an additional line of treatment with CDCT, when the option of HDCT was present as the first salvage treatment.**

**We eagerly await the results of the TIGER trial, which would be pertinent at helping answer many of these questions. Until then, the options of conventional and high dose chemotherapy have to be balanced with a clear discussion between clinician and patient – taking into account the available**

**data, the patient's prognostic factors, residual organ tolerance, and side effects of the proposed treatment regimen.**

**4) Conclusion.**

Dose intense regimens have fallen out and back into favour in the treatment of patients with metastatic testicular cancer who are deemed to have a high risk of failure of conventional treatment. The increased toxicity profile of these regimens necessitates management in high volume centres with expertise in the safe delivery of this type of chemotherapy. With recent randomised data suggesting improved outcomes for patients with poor tumour marker decline, we support renewed interest in this approach, and would suggest that the variety of cytotoxic agents as well as the intensity is key to achieving optimal cure rates. In relapsed disease following cisplatin based chemotherapy the clinician treating testicular cancer has a number of regimens at their disposal with a reasonable chance of cure, including conventional dose and high dose chemotherapy. Despite a lack of conclusive randomised data utilising modern approaches (which is eagerly awaited) it seems likely that some patients will fare better with a second line high dose approach, and some with conventional dose treatment, with a good chance of salvage. It remains for clinicians to utilise the breadth of available data and personalise their approaches to treating patients with metastatic testicular cancer. Where there is a level of equipoise with data we would ensure discussions are had with patients about the benefits and risks of each approach and to involve patients as much as possible in the decision making process. High dose or dose intense chemotherapy is a powerful tool and we would advocate strongly for the individualisation of approach to the patient and their disease.

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