TOPIC PAPER

High-risk clinical stage I nonseminomatous germ cell tumors: the case for chemotherapy

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Abstract Testis cancer is the most frequent solid malignancy in young men. The majority of patients present with clinical stage I disease and about 50% of them are nonseminomatous germ cell tumors. In this initial stage of disease there is a subgroup of patients at high risk with a likelihood of more than 50% for relapse. Treatment options for these patients include: retroperitoneal lymph node dissection (RPLND), albeit 6–10% of patients will relapse outside the field of RPLND, active surveillance with even higher relapse rates and adjuvant chemotherapy. As most of these patients have the chance to become long-term survivors, avoidance of long-term side effects is of utmost importance. This review provides information on the potential of chemotherapy to achieve a higher chance of cure for patients with high-risk clinical stage I disease than its therapeutic alternatives and addresses toxicity and dose dependency.

Keywords Nonseminomatous · Germ cell · Chemotherapy · High risk · Testicular neoplasm

Introduction

The introduction of cisplatin-based chemotherapy has made testis cancer a highly curable disease. Testis cancer represents the most frequent malignant solid tumor in young

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men and 90% of patients present with clinical stage I disease and normal tumor markers after orchiectomy [1]. Of these, half of patients are diagnosed with nonseminomatous germ cell tumor (NSGCT) of the testis. Treatment options include surveillance with deferred chemotherapy in case of relapse, retroperitoneal lymph node dissection (RPLND) or two courses of bleomycin, etoposide and cisplatin (BEP) chemotherapy, but the preferred management of clinical stage I NSGCT still remains controversial. Although therapeutic approaches differ between countries and institutions, there seems to be no difference in the excellent long-term survival rates of 97% or more.

Only 30% of patients have occult metastatic disease found at RPLND, making either routine chemotherapy or RPLND potentially unnecessary therapeutic burdens.

To minimize unnecessary overtreatment, risk stratification for patients at high risk for harboring undetectable metastases were developed in order to administer early adjuvant therapy only to those who most likely need it. Subsequently, a risk-adapted strategy based on the absence or presence of risk factors in the orchiectomy specimen has been recommended as standard procedure [2].

In this review we focus on the role of chemotherapy in patients at high risk to develop metastatic disease and discuss the pros and cons of established alternative treatment options.

Prognostic risk factors

With the exception of choriocarcinoma and yolk sac tumors that metastasize mainly via hematogenous routes, NSGCTs follow a well known and predictable route of metastatic spread based on the lymphatic drainage of the testes to the retroperitoneal lymph nodes, and efforts have been made to

identify metastatic lymph nodes in the retroperitoneum. Computed tomography (CT) is only able to distinguish metastatic nodes by size. Newer imaging techniques such as 18-FDG-PET now have additional ability over CT to detect patients at high risk for relapse [3]. As the presence of occult retroperitoneal metastases cannot be reliably ruled out due to inaccuracy of clinical staging methods, multiple studies have been conducted to identify risk factors for pathologic stage II A disease.

In 1987 a multivariate analysis performed by the Medical Research Council (MRC) identified four histopathologic features of the primary tumor that predicted relapse: vascular invasion, lymphatic invasion, absence of yolk sac elements and presence of undifferentiated tumor [4]. On the basis of these features another MRC trial was conducted that showed a recurrence rate of approximately 50% when three or four of these risk factors were present with vascular invasion (VI) being the most important [5].

In a prospective trial of the German Testicular Study Group, 200 patients were assigned to RPLND [6]. Twenty-eight percent of patients were found to have retroperitoneal disease and again VI was the most predictive variable with a positive predictive value (PPV) of 52.7%. This was increased to 63.7% by adding the MIB score $\geq$70% and percentage of embryonal carcinoma (EC) >50%. Patients at low risk for relapse could be identified with a negative predictive value of 86.5%, rendering them good candidates for surveillance.

Moul et al. analyzed 92 patients with clinical stage I NSGCT for histological risk factors. The probability of occult disease rose from 4% in patients without embryonal components and no VI to 67% in patients with 50% EC and VI, and up to 92% in patients with pure EC and VI. This gave an almost linear relationship between the percentage of EC and retroperitoneal disease [7]. Other models confirmed the influence of percentage of EC ($\leq$45%, 46–79%, $\geq$80%) and VI, with odds ratio (OR) of 2.1–7.4 and 8.2–9.0 for the percentage of EC 46–79% and $\geq$80%, respectively [8, 9].

Similar results were published by the Indianapolis group who reported a 46.5% risk of pathological stage II disease when EC predominance and VI were present in the orchiectomy specimen [10].

Several study groups showed that VI, higher pT-stage (pT2–4 vs. pT1) and EC predominance were most predictive of pathological stage II and the risk of recurrence ranged between 32 and 76%. In a meta-analysis pT-stage and presence of embryonal carcinoma had moderate effects, but MIB-1 staining >70% was a promising predictor for relapse (OR 4.7) [11]. Other molecular markers such as p53, bcl-2, cathepsin D and E-cadherin have little predictive value when compared to VI [8].

In summary, several risk factors have been identified; VI and EC are the most powerful predictors for relapse allowing for a risk-adapted treatment. High-risk groups bear a risk of recurrence of approximately 50–60% and low-risk groups of 13–16%.

Evolution of primary chemotherapy in high-risk clinical stage I NSGCT

Patients with clinical stage I NSGCT and a high risk of relapse may be cured with chemotherapy. In Europe two courses of BEP are considered the standard treatment option [2]. With this therapeutic approach cure rates of about 98% are reached.

In 1992 Oliver published the first results of two courses of BEP chemotherapy for patients at intermediate and high risk to develop metastatic disease. Adjuvant chemotherapy was offered when two or more of the high-risk features—VI, lymphatic invasion, presence of undifferentiated cells, absence of yolk sac tumor elements—were presented. Twenty-one of 22 patients (95.5%) remained free of metastases. One patient relapsed and died of progressive disease [12].

One year later Studer et al. presented the medium-term results of two courses of adjuvant BEP in a larger series and longer follow-up of patients with clinical stage I NSGCT. In this trial VI, stage >pT1 or the presence of EC were risk factors required for patient eligibility. After a median follow-up of 42 months 40 of 41 patients (97.6%) remained relapse free. One patient underwent surgical excision of mature teratoma 26 months after orchiectomy and was disease-free thereafter [13]. These results were updated by Bohlen in 1999 [14].

An Austrian group administered two cycles of BEP polychemotherapy in patients with clinical stage I NSCGT and evidence of VI in the primary tumor [15]. After a median follow-up of 79 months 2 of 29 (6.9%) patients had relapsed and one of them died of progressive disease.

In a multicenter UK Medical Research Council study presented in 1996, 114 eligible patients featuring at least three of the four risk factors (VI, lymphatic invasion, presence of undifferentiated cells, absence of yolk sac tumor elements) received two cycles of BEP [16]. Only two relapses were reported after a follow-up of at least 2 years.

The Spanish Germ Cell Group confirmed these data in a well conducted prospective trial in which 589 patients entered a risk-adapted protocol after orchiectomy. Two hundred and thirty-one patients with the high-risk factors of VI or local infiltration of adjacent structures received two courses of BEP, while patients at low risk for relapse were kept under surveillance. In the chemotherapy group two

patients (0.9%) relapsed, and both are disease-free after salvage therapy [17].

Similar results were published by Klepp, Ondrus, Hendry, Boehlen, Chevreau and Amato with 34, 18, 60, 60, 40 and 76 patients at high risk for occult metastatic disease. Risk factors were slightly different from study to study but included mainly the accepted histologic features known to be predictive for relapse. Recurrences occurred in 0–3% of cases with excellent long-term survival rates [14, 18–22]. The Medical Research Council piloted a new regimen with two courses of cisplatin, vincristine and bleomycin (BOP) in clinical stage I high-risk patients intending to eliminate the toxicities of etoposide. The 5-year relapse-free rate of 98.3% in 115 patients was equivalent to that of the BEP regimen, but neurotoxicity was present in 12% after 2 years and the authors could not show any clear-cut advantages of BOP over the BEP regimen [23].

Hoping to cure patients with a lesser cytotoxic treatment, the Swiss Group for Clinical Cancer Research recently completed a protocol with one single course of BEP chemotherapy for high-risk clinical stage I NSGCT [24]. After a median follow-up of 99 months, 36 of 37 evaluable patients with VI and/or EC predominance (>50%) remained relapse-free with one possibly treatment-related death with acute respiratory distress syndrome shortly after salvage chemotherapy.

Lately, the German Testicular Cancer Study Group published the results in 382 patients with clinical stage I NSGCT randomized to either RPLND or one cycle of BEP chemotherapy without consideration of risk factors. VI was present in 138 patients (42%) and was evenly distributed between the two treatment groups. The oncological outcome of this high-risk subpopulation was not determined in the study. The overall difference in the 2-year recurrence-free survival rate between chemotherapy and surgery, however, was 7.04% in favor of chemotherapy, and the hazard ratio to sustain tumor relapse with RPLND was 7.937 (95% CI, 1.808–34.48). This is the first randomized trial that proved a superior outcome for one single course of adjuvant chemotherapy over RPLND in clinical stage I NSGCT. Nevertheless, there is a relatively high surgical failure rate after RPLND with seven retroperitoneal and two inguinoscrotal recurrences. Adequacy of RPLND was less than expected in this 61-center trial in which many surgeons performed relatively few procedures. This finding again strongly suggests that RPLND should be performed in specialized high-volume centers only to minimize recurrences.

An overview on the results reported with adjuvant chemotherapy for high-risk clinical stage I NSGCT is presented in Table 1.

Adjuvant chemotherapy in perspective to other treatment modalities

Since success rates of the established treatment modalities surveillance, RPLND and adjuvant chemotherapy are

Table 1 Chemotherapy for with high-risk clinical stage I NSGCT

First author	Year	Chemotherapy	Risk factors	No. of patients (evaluable/all)	Relapse rate[a]	DOD
Oliver [12]	1992	2 BEP	≥2 MRC RF	22/22	1 (4.5%)	1 (4.5%)
Cullen [16]	1996	2 BEP	≥3 MRC RF	109/114	2 (1.8%)	1 (0.9%)
Pont [15]	1996	2 BEP	VI+	29/42	2 (6.9%)	1 (3.4%)
Klepp [20]	1997	3 BEP	VI+ and AFP−	32/34	1 (3%)	0
Ondrus [21]	1998	2 BEP	VI+ and/or ECP	18/18	0	0
Bohlen [14]	1999	2 BEP or PVB	VI+ and/or LI+ and/or ≥pT2 and/or EC+	58/60	1 (1.7%)	0
Hendry [22]	2000	2 BEP	≥3 MRC RF	60/60	1 (1.7%)	1 (1.7%)
Chevreau [19]	2004	2 BEP	VI+ and/or LI+ and/or EC+	36/40	0	0
Amato [18]	2004	CEB	1 or more RF: AFP >80 ng/dl, >80% EC, VI, LI	68/76	1 (1.5%)	0
Maroto [17]	2005	2 BEP	VI and/or EC+ and/or invasion of local structures	231/231	2 (0.9%)	0
Dearnaley [23]	2005	2 PVB	VI+ and/or LI+	115/115	2 (1.7%)	1 (0.9%)
Westermann [24]	2008	1 BEP	VI+ and/or LI+ and/or ECP	37/40	1 (2.7%)	1 (2.7%)
Albers [31]	2008	1 BEP	VI in 41.8% of patients	174/191	2 (1.1%)	0
Total				989/1043	16 (1.6%)	6 (0.6%)

BEP bleomycin, etoposide, cisplatin; *BE* bleomycin, etoposide; *PVB* bleomycin, vincristine, cisplatin; *CEB* carboplatin, etoposide, bleomycin; *PVB* cisplatin, vinblastine, bleomycin; *RF* risk factor; *DOD* dead of disease

Risk factors: *VI* vascular invasion; *LI* lymphatic invasion; *EC* embryonal carcinoma; *ECP* embryonal carcinoma predominance; *MRC risk factors* vascular invasion, lymphatic invasion, absence of yolk sac tumor, presence of undifferentiated cells; *AFP* normal pre-orchiectomy AFP serum level

[a] Contralateral testis cancer excluded

similar, focus has changed toward minimizing treatment-related morbidity by maintaining oncological efficacy.

RPLND is considered the best staging procedure by many US authors and has excellent long-term results and high cure rates, even in case of relapse [10, 25]. Furthermore, it simplifies postoperative follow-up with less frequent abdominal CTs, as recurrence predominantly occurs outside the limits of the surgical templates. Major disadvantages are that about 50% of all high-risk clinical stage I cancers are overtreated with RPLND and that 8–29% of patients experience relapse. This is mainly in the mediastinum, even in case of lymph node-negative disease, indicating that metastases bypass the retroperitoneum [10, 26]. The 29% rate of distant metastases in high-risk patients with EC predominance and VI in the primary tumor following RPLND, despite histologically negative nodes, is far higher than in the low-risk group, where metastases occur in only 4–6% of cases [10, 26]. Therefore, meticulous removal of the retroperitoneal lymph nodes cannot prevent recurrence in all cases and still requires a costly and careful patient follow-up. In addition, as a significant number of patients with clinical stage I–IIA NSGCT and retroperitoneal metastases present with extratemplate disease, an extensive RPLND is a must [27]. Of patients with clinical stage I, but pathological stage IIA disease, 20–40% will relapse if left untreated after RPLND and will require three to four courses of intensive platinum-based induction chemotherapy [28, 29]. In such cases cytotoxic morbidity is increased. Thus, the data from the most experienced centers show that RPLND often is not curative when negative or positive nodes have been removed [30], and the rationale for lymph node dissection in the latter patient group is more than questionable. Furthermore, surgical complications occur in 5–14%. Only in experienced hands are postoperative morbidity and ejaculatory dysfunction rates low. In inexperienced hands recurrence and death after RPLND may occur [31].

Active surveillance in clinical stage I NSGCT is the only way to avoid unnecessary over treatment. Non-risk-adapted surveillance protocols have shown relapse rates of 17–38% due to undetected micrometastases, 17–30% in the retroperitoneum and about 10% above to the diaphragm [4, 5, 32, 33]. In patients with high-risk testicular cancer relapse rates rise to 52–75.7% [32–34], and patients may be under considerable psychological stress due to this. Patients experiencing progressive disease must be exposed to the toxicity of three to four cycles of intensive chemotherapy [22] and despite appropriate salvage therapy, 1–2% of them die of progressive disease. Therefore, surveillance protocols in patients featuring high-risk factors have been abandoned by several authors. In addition, post-chemotherapy RPLND which may be necessary for residual masses after salvage chemotherapy is associated with higher acute morbidity

and reduced preservation of ejaculatory function in 60% of cases [35].

Most relapses occur within the first 2 years after diagnosis. Therefore, high patient compliance is mandatory not only during this early period of time to detect recurrence at an early stage, but also for many years, as 5–10% of patients develop late relapse. Frequent abdominal and thoracic CT or MRI scans are essential for adequate follow-up. In a Canadian multicenter surveillance program the rate of compliance was as low as 64% for CT scanning during the first 2 years [36]. Compliance was highest in centers with protocols requiring the least frequent visits, but especially surveillance programs require close follow-ups.

An additional disadvantage of repeat CT examinations is the exposure of the patients to a considerable radiation dose. After 10 CT scans, which are usually required for a "wait and watch" policy, an estimated 5 of 1,000 men may develop a radiation-induced secondary malignancy. Considering the current and future CT use, the estimated risk may rise to 1.5–2.0% [37]. These data are supported by Chamie et al., who reported on 3,334 patients who chose active surveillance or RPLND for clinical stage I NSGCT. Of these, 172 developed a secondary malignant neoplasm (SMN) after a median follow-up of 16.4 years. Patients under surveillance developed secondary radiation-induced malignancies 1.74 times more frequently than those who underwent RPLND [38]. In addition, also patients without adjuvant therapy face the risk of late toxicity and malignant transformation.

Men with curable testis cancer are long-term survivors. This fact weighs heavily on chemotherapy-related toxicity. Acute and long-term side effects have always strengthened the case against adjuvant chemotherapy and for RPLND, as cisplatin-based cytotoxic treatment is often associated with nephrotoxicity, cardiotoxicity and ototoxicity.

Nephrotoxicity may occur to some degree in patients who receive cisplatin, but it is rare when administered with adequate hydration [14]. Even in patients with disseminated germ cell tumors and poor prognosis treated with high-dose VIP (etoposide, ifosfamide, cisplatin), renal failure is as low as 3% [39]. Nephropathy is compensated with only serum creatinine elevation and no elevation of other retention parameters.

Concerning cardiotoxicity, no association was found between chemotherapy and an increased risk for cardiovascular disease in clinical stage I or II patients treated with surgery alone or surgery and chemotherapy. In addition, no elevated risk for myocardial infarction (MI) in more than 2,500 5-year survivors of testis cancer was reported for BEP chemotherapy alone, whereas the MI risk after PVB (cisplatin, vinblastine, bleomycin) chemotherapy, mediastinal irradiation and recent smoking was increased 1.9, 3.7 and 2.6-fold, respectively [40]. As for ototoxicity, tinnitus

and high-tone hearing loss are reported in 20–40% of patients treated with higher cisplatin doses, but no serious long-term side effects were reported in studies using two BEP cycles for clinical stage I high-risk NSGCT [14–16, 19, 24].

Bleomycin-induced pneumonitis is another rare but well-known problem, especially when smoking is a co-existing risk factor. In testis cancer patients treated with RPLND with or without adjuvant, 3–4 courses of BEP there was no difference in long-term impairment of pulmonary function [41]. To keep pulmonary toxicity as low as possible, in the Swiss BEP protocols bleomycin was given as a 24-h infusion and no lung toxicity was reported [14].

The risk for etoposide induced secondary leukemia is an often cited argument against the use of BEP for NSGCT. Several studies show a risk of 0.5–1% with cumulative high-dose etoposide doses >2–8 g/m^2 [42]. Modern BEP regimens remain significantly below this threshold, and no leukemia was reported at doses <2 g/m2, rendering leukemia a negligible concern for NSGCT patients.

The risks of secondary solid malignancies (SMN) in 2,700 5-year survivors of testis cancer were calculated by van den Belt-Dusebout. In NSGCT patients receiving chemotherapy alone, the standardized incidence rate for SMN was 1.4 (0.9–2.1) compared to patients with surgery alone. However, patient data were collected from the period 1965–1995 when treatment protocols with two or less cycles of BEP were not used, and patients were treated with high-dose chemotherapy. Furthermore, the risk of melanoma, which was the predominant SMN followed by bladder cancer, was increased not only after chemotherapy alone, but also after other treatments. This suggested shared genetic origins with NSGCT instead of treatment causality [43].

Furthermore, it is unknown whether the development of a secondary neoplasm is related to an inherent genetic instability which also originated the testicular cancer [44].

Usually, patients with testis cancer are young at the time of diagnosis, and fertility is an important aspect. It is known that 50–70% of testis cancer patients are subfertile or have impaired spermatogenesis, and even on surveillance alone pregnancy rates are as low as 46%, because gonadal dysfunction is common in these patients. After 3–4 cycles of BEP for advanced disease semen quality normalizes following intermittent depression. When only two courses of chemotherapy are given there is no negative affect on sperm counts after 9–12 months [15, 16].

An important argument against adjuvant chemotherapy is the risk of metastatic adult teratoma to the retroperitoneum, even if absent in the primary tumor. Teratoma is a histologically benign slow growing tumor that is resistant to chemotherapy, and treatment requires complete surgical excision. Metastatic spread is rare (3%) in clinical stage I NSGCT [45], and resection is possible before teratomatous masses cause compression of neighboring structures and before a late relapse with malignant transformation occurs. Another point against adjuvant chemotherapy is the risk of aggressive late relapses in the retroperitoneum. However, these are only related to the initial tumor burden and occur after chemotherapy for bulky metastatic disease at first presentation of patients [46] suggesting incomplete eradication and selection of chemotherapy-resistant cells. Chemoresistant relapse in clinical stage I NSGCT has not been reported so far [47].

Once patients at high risk for relapse are identified, occult metastatic disease can be treated by chemotherapy. The advantage of this strategy is based on the fact that tumor burden is never as small as right after orchiectomy and therefore the quantity of cytotoxic drugs necessary can be reduced to a minimum.

Until now all studies approaching high-risk clinical stage I NSGCT with two courses of chemotherapy such as BEP have been shown to eliminate virtually all occult metastases and to produce excellent survival rates of 98–99%. Long-term toxicity remains marginal [15, 19, 24] and poor compliance is negligible, since relapse—in contrast to RPLND or surveillance—is an exception. In addition, double treatment with higher dose salvage chemotherapy after failure of primary RPLND can be avoided.

These are the reasons why the European Consensus Conference on diagnosis and treatment of germ cell cancer suggests two cycles of adjuvant BEP for patients with high-risk clinical stage I as a standard [2]. Studies are underway to elucidate whether even 1 cycle of BEP is sufficient as has been suggested by preliminary data. [24–26]

Conclusion

Patients with clinical stage I NSGCT at high risk for relapse have an excellent long-term prognosis independent of the therapeutic approach used. Surveillance protocols leave the patients with approximately a 50% risk for relapse. This exerts a high psychological pressure on patients and extensive chemotherapy in case of relapse if necessary. RPLND alone is not curative if positive nodes are found and leaves the patient with a 6–10% risk of progression even if the nodes are negative. This implies not only substantial overtreatment for the majority of patients who do not profit from RPLND. Patients may also be exposed to unnecessary morbidity combined with an uncertain cure. In case of extratemplate recurrence high-dose salvage chemotherapy is needed. With the intention to minimize morbidity and maximize efficacy, two courses of adjuvant chemotherapy have turned out to be the best for reaching the goal of cure. Therefore, risk-adapted management with adjuvant

chemotherapy for high-risk patients with clinical stage I NSGCT seems appropriate. Efforts are being made to further reduce toxicity, and the application of just one single course of BEP may turn out to be the future standard if ongoing trials confirm existing results.

Conflict of interest statement   There is no conflict of interest.

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