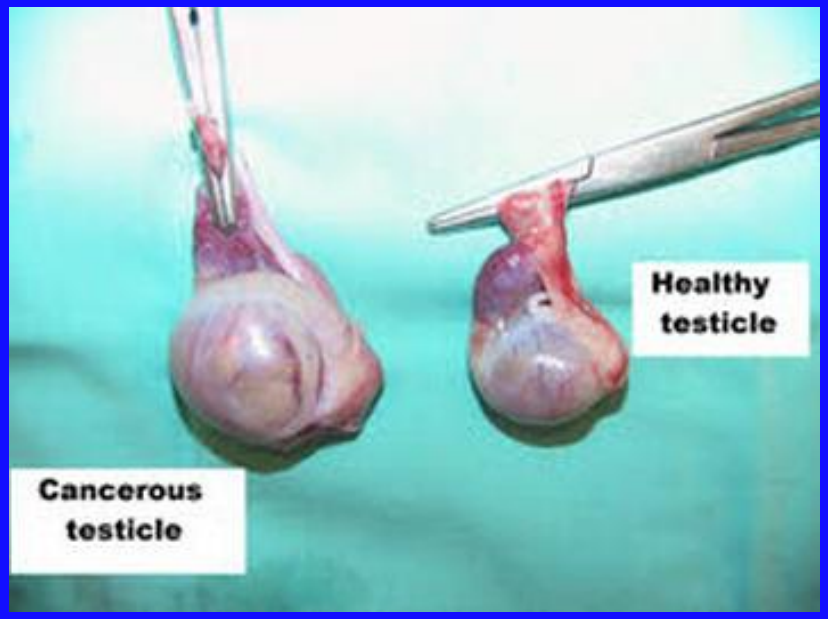
Testis tumors



Richard Epstein

TKCC/SVH, August 5 2016

Cis-Diamminedichloroplatinum, Vinblastine, and Bleomycin Combination Chemotherapy in Disseminated Testicular Cancer

LAWRENCE H. EINHORN, M.D., F.A.C.P.; and JOHN DONOHUE, M.D.; Indianapolis, Indiana

Fifty patients with disseminated testicular cancer were treated with a three-drug combination consisting of *cis*-diamminedichloroplatinum, vinblastine, and bleomycin. Three patients were considered inevaluable due to early death. This chemotherapy regimen produced 74% complete and 26% partial remissions. Furthermore, five patients with partial remission became disease-free after surgical removal of residual disease, producing an overall 85% disease-free status. Toxicity, although significant during remission induction with *cis*-platinum, vinblastine, and bleomycin, was usually manageable, although there were two drug-related deaths during this period. Thirty-eight of these patients remain alive and 32 remain alive and disease-free at 6+ to 30+ months. We believe this regimen represents a major advance in the management of patients with disseminated testicular cancer.

ALTHOUGH TESTICULAR CANCER accounts for only 1% of all malignant tumors in men, it ranks first in incidence of cancer deaths in the 25 to 34 age group (1). Thus cancer of the testis has a significant impact on the social, economic, and emotional status of this young population.

Radiotherapy is the treatment of choice for pure seminoma, as this tumor is very radiosensitive, producing a 90% to 95% cure rate, and retroperitoneal node dissection is rarely indicated (2). Indeed, radiotherapy for metastatic lesions produces an excellent 55% 5-year survival (3). However, the treatment for nonseminomatous germinal neoplasms has produced much less satisfactory results with considerably more controversy as to the preferred treatment for all stages of disease.

In 1960, Li and associates (4) introduced the first major thrust of chemotherapy in advanced testicular cancer with the combination of dactinomycin (actinomycin-D), chlorambucil, and methotrexate. Subsequent studies confirmed a 50% to 70% response rate, which included 10% to 20% complete remissions (5, 6). The past 15 years have also seen the development of many new agents with substantial activity, notably vinblastine (7), bleomycin (8), and mithramycin (9). One of the major significant achievements of these single-agent studies was not only the demonstration that a complete remission could be obtained in disseminated testicular cancer, but that approximately half of these complete remissions were permanent cures (5-7, 9). Most relapses occurred within 2 years of initiation of chemotherapy.

Combination chemotherapy has produced excellent long-term complete remissions in other chemosensitive tumors such as Hodgkin's disease (10). Likewise, most recent attempts at improved chemotherapy in testicular cancer have been with combination chemotherapy. One of the most widely used combinations has been vinblastine plus bleomycin (11).

Cis-diamminedichloroplatinum is one of a group of coordination compounds of platinum identified by Rosenberg, VanCamp, and Krigas (12) that strongly inhibits bacterial replication. This agent has significant activity in refractory advanced testicular cancer, and, furthermore, it is ideal for combination chemotherapy because of its relative lack of myelosuppression (13).

In 1974, we began a study using vinblastine, bleomycin, and *cis*-diamminedichloroplatinum in disseminated testicular cancer. The primary goal was to increase the complete remission rate and potential cure rate. The results of treatment of the first 50 patients are the subject of this paper.

Materials and Methods

Fifty patients with germ-cell tumors of the testis were the subjects of this study. The median age was 26 years with a range of 15 to 63. All patients with metastatic measurable disease not refractory to any of the study agents were eligible for this study. Three patients died within 2 weeks of initiation of chemotherapy and were considered inevaluable.

Platinum was given in a dosage of 20 mg/m² body surface area as a 15-min intravenous infusion for 5 consecutive days (Days 1 to 5) every 3 weeks for three courses. Eight patients were given additional courses of platinum because they had no significant nephrotoxicity and had persistent evidence of residual disease after the first three courses. Vinblastine was given on Days 1 and 2 in a total dosage of 0.4 mg/kg body weight (0.2 mg/kg body weight each day) for a total of five courses every 3 weeks, and then given as a single injection in a dosage of 0.3 mg/kg body weight every 4 weeks for a total of 2 years of therapy. The vinblastine dosage was lowered 25% if the patient received previous radiotherapy. Bleomycin was given on Days 2, 9, and 16 of each platinum course, and was given with the platinum 6 h after vinblastine and then given weekly for a total of 12 weeks in a dosage of 30 U per week by intravenous push injection. Vinblastine and bleomycin were used in sequential

▶ From the Indiana University Medical Center; Indianapolis, Indiana.

Testis cancer

- Remains virtually the only solid (non-haematologic) metastatic tumour that is routinely curable by drug therapy.

What we will discuss

1. Epidemiology of testis tumors
2. Clinical aspects of testis tumors
3. Molecular biology of testis tumors
4. Management of testis tumors

1. Epidemiology of testis tumors

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Incidence rising (esp. Caucasians, e.g. Danish > 1%)

African-Americans lower risk; Maoris higher risk

Cohort-dependent: WW2 births have low incidence

Doubling of Western incidence over last 35 years

Five-fold higher incidence in 1st- vs. 3rd-world

Migrant studies ➔ environmental effect (?in utero)

50% pts present between ages 20-35 (median = ?)

Seminoma rate increase > NSGCTs; young > old

1. Epidemiology of testis tumors

Rising TGCTs parallels falling sperm counts

TGCTs predisposed to by cryptorchidism (10% all)

Orchiopexy delayed until after puberty is riskiest

Mildly associated with height (not weight/BMI)

Usu. associated with CIS/ITGCN (or microlithiasis)

Higher risk (5x) with 1st-degree relative (?genetic)

Commoner (2-5%; 12x) if other testis affected. TSE.

Prognosis worse for older age of onset

2. Clinical aspects of testis tumors

2. Clinical aspects of testis tumors

Usually presents as a painless mass

7% gynecomastia (↑ bHCG) - usually NSGCTs

Rarely associated with precocious puberty

Investigation: U/S, AFP/HCG/LDH, CT abdo/pel/chest

Surgery: transinguinal orchiectomy

RPLND

Metastasectomy

2. Clinical aspects of testis tumors

Prognosis

- 95% all testis Ca is curable
- 80% metastatic disease is curable
- Low volume disease – generally better Px

Advanced disease

- Intermediate risk
- Poor risk

2. Clinical aspects of testis tumors

Histology:

Pure seminoma (60%)

- bHCG elevated in 25% pre-orchiectomy

- Better Px than NSGCT

NSGCT

- AFP, bHCG, LDH often elevated

Leydig cell tumours, etc.

Non-germcell tumors, e.g. lymphoma, metastases

2. Clinical aspects of testis tumors

Serum tumour markers:

AFP – half-life (post-orchiectomy) 5-7 days

bHCG – half-life 2-3 days

Slow marker decline during chemo in “poor-prognosis” patients on BEP may indicate need to intensify Rx

Uniquely in oncology, serum tumour marker levels are used for TGCT ***staging*** (S0-3); e.g., for S3, AFP > 10,000 *or* HCG > 50,000 (*or* LDH > 10x ULN)

2. Clinical aspects of testis tumors

Staging:

TNM – see ESMO or NCCN guidelines

75% seminoma and 50% NSGCTs are stage I

2. Clinical aspects of testis tumors

Prognostic (IGCCCG) categories:

Seminoma

"Good" – 90%; excludes non-lung visceral mets

"Intermediate" – 10%: non-lung visceral mets

bHCG level is *not* prognostic (AFP excludes Dx)

NSGCTs

"Good" – 60%; lowish markers; testis/RP origin

"Intermediate" – 30%; intermediate markers

"Poor" – 10%; S3 markers *or* mediastinal primary *or* non-lung visceral mets (45% 5YS)

2. Clinical aspects of testis tumors

Extragonadal primary GCT:

- Mediastinal NSGCT: BEP x4
- Mediastinal seminoma: BEP x4, or BEP x3 then RT
- Surgical resection for residual disease or marker +

Sacrococcygeal GCTs – poor Px (30% 5YS)

Intracranial GCTs – BEP +/- RT for seminomas

Retroperitoneal EGGCT: same as for testis primary

2. Clinical aspects of testis tumors

Role of FDG-PET scanning:

Controversial; ***not*** routinely indicated in TGCTs

But *can* be useful in assessing residual nodal masses in the absence of marker elevation (differentiated teratoma suspected) particularly in *seminomas* with residual nodes > 3cm size.

3. Molecular biology of testis tumors

- Linked to Klinefelter's syndrome (esp. primary mediastinal GCT) and Down syndrome (seminoma only)
- Polygenic (GWAS-defined) inherited genetic factors account for 50% disease risk
- Tumours stem from noninvasive fetal precursor cell(s) that lie dormant during childhood/adolescence (ITGCN)
- Hormonal surge at puberty may trigger malignant transformation of ITGCN; *KIT* mutations in 25% semin's
- ITGCN-to-seminoma transformation upregulates sperm genes, incl. *PRAME*, *MAGEA4* (PGCs)
- ITGCN-to-NSGCT transition via ↑*SOX2/DNMT3B*

3. Molecular biology of testis tumors

- The main tumorigenic driver pathway so far recognised is KIT, but little therapeutic impact to date
- Heterozygous KIT-LG (‘stem cell factor’) lesions at 12q21 cause upregulation of KIT (ligand) signalling
- *SPRY4* suppressor gene lesions (5q31) enhance ERK
- Gene point mutations are rare. In particular, the *TP53* gene is usually wild-type, consistent perhaps with the chemosensitive and chemocurable phenotype of TGCT. (*XRCC* and *ERCC2* defects also mooted to explain this).
- Chromosomal gains (aneuploidy, CNVs) common, esp. that of 12p – isochromosome 12p is a hallmark of TGCTs.

4. Management of testis tumors

4. Management of testis tumors

Seminoma Mx

- stage 1 – often surveillance
  - 15-20% relapse (RPLNs), < 3 years
  - earlier Dx (↑ CTs) may permit RT use
- stage 2 – chemo (or RT)
  - RT less popular now due to toxicities
  - viz., CVD/RAS, 2nd cancers (2x)
- stage 3 presentations uncommon

4. Management of testis tumors

Seminoma Mx

- Single-dose carbo AUC 7 for stage 1 (Oliver)

Risk factors:

> 4cm size (HR 2.5)

Stromal rete invasion (HR 2)

No risk factors: 5Y relapse 2% (carbo), 4% (observn)

Risk factors +: 5Y relapse 9% (carbo), 15% (observn)

Carbo x2 doses: does not seem much more effective

Bulky RPLN relapse > 5cm? Chemo > RT

RT? Older patients wishing to avoid chemo toxicity

4. Management of testis tumors

Residual nodal masses

Seminoma:

After CT/RT? Often fibrosis/necrosis

FDG-PET can help select to resect:

FDG-non-avid, or < 3 cm? Just observe

Cf. post-*NSGCT* masses (30%): often Ca, teratoma

Hence, resect (if > 3cm and not involving major vessels), i.e. post-chemo Sx (PCS)

4. Management of testis tumors

NSGCT

CS 1? But 30% relapse, usually in RPLNs

High-risk CS 1 prognostic factors:

- Pure embryonal (50% relapse) or embryonal-dominant (>50% tumour)
- LVI (50% relapse)
- Proliferation rate > 70%

No LVI? Only 15% relapse

Most relapses occur in first 2 years

4. Management of testis tumors

RPLND

- Mainly used in USA, but now *less used*
- Both diagnostic and therapeutic
- Said to obviate need for scan follow-up
- May also obviate adjuvant chemo need

4. Management of testis tumors

Chemo: adjuvant for high-risk NSGCT

"2 cycles BEP" (NCCN); 1 cycle (ESMO)

No level 1 data showing OS benefit when compared to surveillance and treat on relapse

SWENOTECA study: 1 cycle BEP

reduced relapse rates by 95%

Note that *sperm banking* must be recommended (or declined) prior to any chemotherapy

4. Management of testis tumors

Chemo: metastatic presentations

“Good risk disease”: 3 BEP or 4 EP if bleo c/i

“Intermediate/poor risk disease”: 4 BEP

Poor-risk disease – refer to TGCT specialty centre

Recurrence following adjuvant BEP? More BEP…

4. Management of testis tumors

Chemo: general

Guideline orthodoxies:

Don’t reduce cycle dose-intensity (delay)

Don’t give G-CSF unless prior sepsis

Follow marker decline (online calculator)

4. Management of testis tumors

Bleomycin

‘Radiomimetic’ – cuts DNA into ssDNA

Frequent *febrile* reactions 1st 24hrs post-bleo

Lung toxicity in > 10%, may be fatal, esp. older

Potentiated by cis-DDP-induced nephrotoxicity

Commoner if total bleo dose > 400 U

Repeat RFTs prior to each cycle; toxicity after 4/12

Watch DLco and TLC; no consensus on utility

Steroids *may* help acute toxicity; *may* be reversible

4. Management of testis tumors

Refractory/recurrent (platinum-resistant) disease

- Tends to be *de novo* (“poor risk”)
- Molecular basis still unclear
- ? Epigenetic changes acquired
- KRAS upregulation c/w i12p
- *CCND1* amplification
- *PIK3CA/AKT1/FGFR3* mutations

4. Management of testis tumors

Testis Ca: follow-up surveillance guidelines

Controversial and varies Europe vs. USA

CT every 6/12 for 2-3 years; 1st scan at 3 months.

(But varies with clinical suspicion/Px)

Previous chemo/RT? CT *once* per year

MRI pelvis can be substituted, but costly

Chest CT – use for NSGCT, less vital for seminoma

4. Management of testis tumors

Refractory/recurrent (platinum-resistant) disease

RT for seminoma in RPLNs alone

RPLND for NSGCT localised to this site

Pulmonary metastasectomy

Salvage chemo, e.g. VIP, paclitaxel/ifosfamide

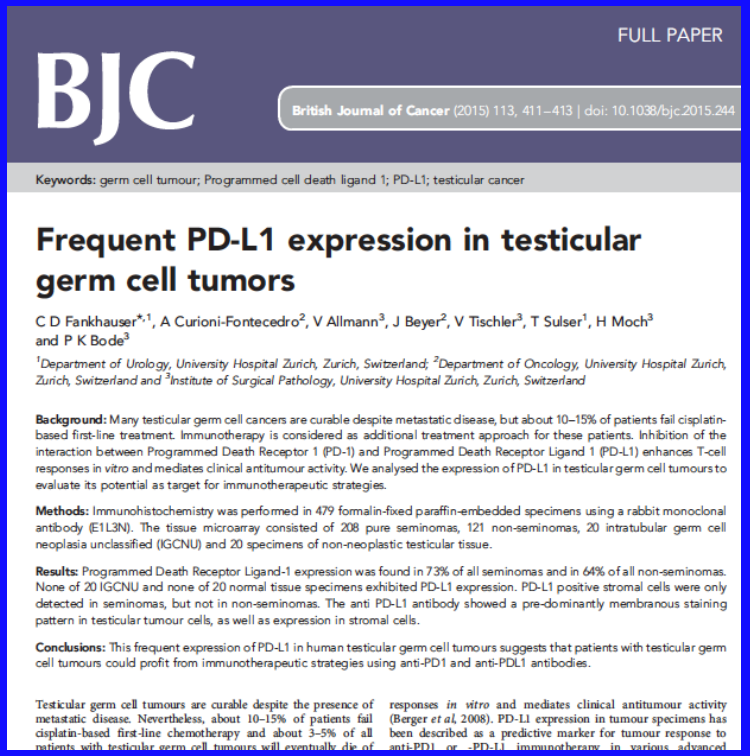
High dose (marrow transplant)

4. Management of testis tumors

New and unproven treatments

- Imatinib for *KIT*-mutant TGCTs
  - "Didn't work" thus far
  - ? Need to use in combination with…?
- Immunotherapy

4. Management of testis tumors



FULL PAPER

BJC

British Journal of Cancer (2015) 113, 411–413 | doi: 10.1038/bjc.2015.244

Keywords: germ cell tumour; Programmed cell death ligand 1; PD-L1; testicular cancer

Frequent PD-L1 expression in testicular germ cell tumors

C D Fankhauser*[,1], A Curioni-Fontecedro[2], V Allmann[3], J Beyer[2], V Tischler[3], T Sulser[1], H Moch[3] and P K Bode[3]

[1]*Department of Urology, University Hospital Zurich, Zurich, Switzerland;* [2]*Department of Oncology, University Hospital Zurich, Zurich, Switzerland and* [3]*Institute of Surgical Pathology, University Hospital Zurich, Zurich, Switzerland*

Background: Many testicular germ cell cancers are curable despite metastatic disease, but about 10–15% of patients fail cisplatin-based first-line treatment. Immunotherapy is considered as additional treatment approach for these patients. Inhibition of the interaction between Programmed Death Receptor 1 (PD-1) and Programmed Death Receptor Ligand 1 (PD-L1) enhances T-cell responses in *vitro* and mediates clinical antitumour activity. We analysed the expression of PD-L1 in testicular germ cell tumours to evaluate its potential as target for immunotherapeutic strategies.

Methods: Immunohistochemistry was performed in 479 formalin-fixed paraffin-embedded specimens using a rabbit monoclonal antibody (E1L3N). The tissue microarray consisted of 208 pure seminomas, 121 non-seminomas, 20 intratubular germ cell neoplasia unclassified (IGCNU) and 20 specimens of non-neoplastic testicular tissue.

Results: Programmed Death Receptor Ligand-1 expression was found in 73% of all seminomas and in 64% of all non-seminomas. None of 20 IGCNU and none of 20 normal tissue specimens exhibited PD-L1 expression. PD-L1 positive stromal cells were only detected in seminomas, but not in non-seminomas. The anti PD-L1 antibody showed a pre-dominantly membranous staining pattern in testicular tumour cells, as well as expression in stromal cells.

Conclusions: This frequent expression of PD-L1 in human testicular germ cell tumours suggests that patients with testicular germ cell tumours could profit from immunotherapeutic strategies using anti-PD1 and anti-PDL1 antibodies.

Testicular germ cell tumours are curable despite the presence of metastatic disease. Nevertheless, about 10–15% of patients fail cisplatin-based first-line chemotherapy and about 3–5% of all patients with testicular germ cell tumours will eventually die of

responses *in vitro* and mediates clinical antitumour activity (Berger *et al*, 2008). PD-L1 expression in tumour specimens has been described as a predictive marker for tumour response to anti-PD1 or -PD-L1 immunotherapy in various advanced

4. Management of testis tumors

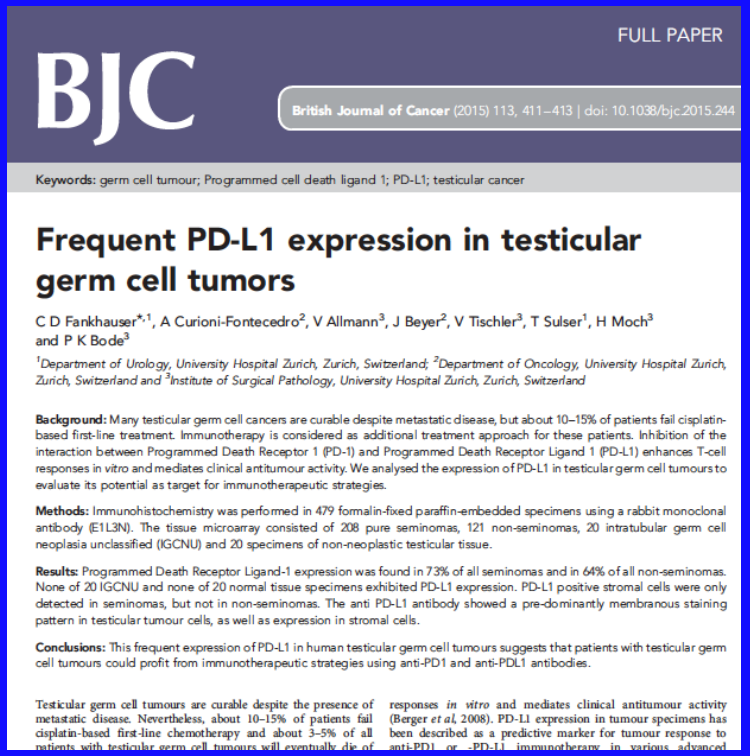


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Table 1. Summary of PD-L1 expression for individual tissue types, tumour components and tumour stage

Tissue types	Negative	Weak	Strong	Positive cases (%)
Seminoma ($n=208$)	57	67	84	73%
Non-seminoma ($n=121$)	43	35	43	64%
Intratubular germ cell neoplasia	20	0	0	0%
Normal testis	20	0	0	0%
Individual tumour components				
Seminomatous ($n=248$)	77	77	94	69%
Choriocarcinoma ($n=10$)	2	2	6	80%
Yolk sac tumour ($n=48$)	29	12	7	40%
Embryonal carcinoma ($n=87$)	34	29	24	61%
Teratoma ($n=46$)	39	5	2	13%
Tumour stage				
pT1 ($n=352$)	164	83	105	53%
pT2 ($n=94$)	32	38	24	66%
pT3 ($n=10$)	3	3	4	70%

4. Management of testis tumors

Long-term morbidities of TGCT treatment

- Sub-/infertility (low sperm; may pre-exist)
- Sperm damage may persist 2 years post-CT
- Sexual dysfunction (hypogonadism, ↓ DHT)
- Metabolic syndrome, cardiovascular disease
- Lung fibrosis, restrictive lung disease
- Neuropathy, nephrotoxicity, ototoxicity
- *GSTP1* SNPs linked to platinum toxicities

4. Management of testis tumors

Second malignancies

Affect 30-40% over 40 years

(cf. general population: 25%)

esp. Leukaemias (earlier onset)

Even more frequent after RT

…the end