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A Single Centre Retrospective Analysis of Toxicity, Prognostication and Oncological Outcomes in Clinical Stage One Seminoma Treated with Carboplatin

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Abstract

Aim: The aim of this retrospective study was to investigate the clinical role and side effect profile of adjuvant carboplatin in patients with clinical stage one seminoma. **Methods:** Twenty four patients with stage one seminoma who were treated with carboplatin were assessed retrospectively. **Result:** 54% (13/24) of patients experienced no acute toxicities with carboplatin.17%(8/24) had grade 1 myelosupression, 8% (2/24)had fatigue and 4%(1/24) had epididymo-orchitis.In terms of long-term toxicities due to carboplatin; 67% (15/24) were well at follow up,13% (3/24) had gastrointestinal toxicity,8% (2/24) had pulmonary changes ,4% (1/24)had grade two fatigue,4%(1/24) had a cardiac event and 4%(1/24) had erectile dysfunction.17% (4/24)had high risk histologic features with a tumour size greater than 4 cm and rete testis involvement.4% (1/24) patient had recurrent disease. 4% (1/24) patient had a second malignancy. All patients were alive at follow up. **Conclusions:** Our findings suggest that carboplatin is a safe and well tolerated alternative to Active Surveillance in a selected group of patients.

Keywords: active surveillance, carboplatin

1. Introduction

Testicular germ cell tumours (GCTs) are the most common malignancy in men between the ages of 15 and 35. GCTs most commonly arise in the gonads, but they may also originate in the retroperitoneum or mediastinum. These exquisitely chemosensitive tumours result in treatment with curative intent regardless of the extent of the disease, with survival rates in Ireland estimated at 96.3% (National cancer registry Ireland, 2012). There are 176 new cases of testicular cancer diagnosed per year in Ireland and the incidence rate is increasing (National cancer registry Ireland, 2012). While the incidence of GCTs in Europe is 6.3/ 100,000 /year (Wilkinson & Read, 1997), Ireland is amongst the highest incidence rates of 7.3/ 100,000/year (National cancer registry Ireland, 2012). Definition of stage and risk classification must be done according to the UICC/American Joint Committee on Cancer (AJCC) and IGCCCG classification (Table 1) (Wilkinson & Read, 1997). Clinical stage one testicular seminoma has a survival rate over 99% (National cancer registry Ireland, 2012; Oldenburg, Martin, & Fossa, 2006). Current guidelines recommend active surveillance as the mainstay of treatment (National Comprehensive cancer network, 2015).The primary endpoint that this study sought to establish was to assess safety and side effect profile of carboplatin use in stage 1 seminoma. Secondary endpoints include the analysis of incidence of disease recurrence, risk of secondary malignancies and the role of histological features in predicting outcomes.

It has been estimated that 70% of patients with testicular seminoma present with stage one disease (National cancer registry Ireland, 2012). After radical orchiectomy, standard treatment options include surveillance, adjuvant radiation to para-aortic lymph nodes or one cycle of single agent carboplatin. Surveillance is the preferred treatment strategy with a risk of relapse of 15-20% at 5 years with the majority of recurrences arising in the infradiaphragmatic lymph nodes (Schmoll et al., 2010; Groll, Warde, & Jewett, 2007; Aparicio et al., 2003; Warde et al., 2002). Overall survival however approaches 100% regardless of the management strategy employed (Chung et al., 2002; Kollmannsberger et al., 2015).

Radiation therapy may be associated with long term cardiac toxicities though this has improved with advances in the delivery of radiation and smaller radiation fields. It has also been associated with secondary malignancies and is contraindicated in inflammatory bowel disease and horseshoe kidneys. Thus one or two cycles of

carboplatin chemotherapy may be a reasonable alternative (Cohn-Cedermark, Stahl, & Tandstad, 2015). Treatment with carboplatin has been shown to be non-inferior to radiation and has similar relapse rates (Dieckmann et al., 2000; Oliver et al., 2011; Mead et al., 2011).

Table 1. Staging of seminoma according to UICC/AJCC and IGCCCG classification

Clinical stage	TNM (UICC/AJC) category					Serum tumour markers (S)			IGCCCG prognostic group[c]
	T		N	M	S	LDH[a]	β-HCG (mIU/ml)[b]	AFP (ng/ml)	
0	pTis	Intratubular germ cell neoplasia	N0	M0	–	–	–	–	NA
IA	pT1	Limited to testis and epididymis, without vascular/lymphatic invasion; tumour may invade into the tunica albuginea but not the tunica vaginalis	N0	M0	S_{any}	Any level	Any level	Normal	NA
IB	pT2	Limited to testis and epididymis, with vascular/lymphatic invasion or tumour extending through the tunica albuginea with involvement of the tunica vaginalis	N0	M0	S_{any}	Any level	Any level	Normal	NA
	pT3	Invasion of spermatic cord							
	pT4	Invasion of scrotum							
IIA	T_{any}		N1 (≤2 cm)	M0	S_{any}	Any level	Any level	Normal	NA
IIB	T_{any}		N2 (>2–5 cm)	M0	S_{any}	Any level	Any level	Normal	NA
IIC	T_{any}		N3 (>5 cm)	M0	S_{any}	Any level	Any level	Normal	Good
IIIA/B/C	T_{any}		N_{any}	M1a (non-regional nodal and/or pulmonary metastases)	S_{any}	Any level	Any level	Normal	Good
IIIC	T_{any}		N_{any}	M1b (liver, bone, CNS or other visceral metastases, e.g. intestinum or skin; ± pulmonary metastases)	S_{any}	Any level	Any level	Normal	Intermediate
IIIC	Mediastinal primary		N_{any}	M_{any}	S_{any}	Any level	Any level	Normal	Intermediate

[a]N indicates the upper limit of normal for the LDH assay.

[b]Cave: β-HCG levels are given in mIU/ml; to convert to ng/ml divide by factor 5.

[c]Poor prognosis is not applicable in seminoma.

LDH, lactate dehydrogenase; HCG, human chorionic gonadotropin; CNS, central nervous system; NA, not applicable.

Currently the NCCN recommends against using a risk adapted approach whereby histologic features are used to make treatment decisions. Studies have been conflicting with regards to the role of histologic features. Surveillance trials highlight tumour size exceeding 4cm and rete testes infiltration as the major risk factors for relapse (Aparicio et al., 2003), however follow up studies have not proven these as reliable predictors of recurrence (Chung & Warde, 2011; Oliver et al., 2005).

After primary treatment NCCN guidelines recommend a surveillance schedule consisting of physical exam, tumour markers and CT abdomen/pelvis every 3-4 months for the first 2 years then every 6-12 months annually thereafter (Chung et al., 2010).

2. Methods

We performed a single centre retrospective review of all patients with stage 1 seminoma who were treated with carboplatin between 2007 and 2010.1 patient received radiation which was poorly tolerated before proceeding to carboplatin. The decision to proceed with two cycles of carboplatin was based on an informed, collaborative, decision making process whereby the benefits of surveillance versus treatment, the risk of relapse, follow up requirements and patient preference were reviewed. All patients selected carboplatin as part of a documented collaborative decision making process and all were offered sperm cryopreservation.

Data was extracted from multiple sources including pharmacy records, patient notes, HIPE and pathology records. Information was recorded on age, dose ie area under the curve(AUC) dose, number of cycles, comorbidities, acute and long-term side effects of treatment,rate of recurrent disease and secondary malignancies. Information on long term survival was also obtained.

3. Results

24 patients were included in our analysis. Median follow up was 5 years. The majority of patients were aged between 20-40 years (71%, 17/24 patients) and had no comorbidities (84%, 20/24) (Table 2). 84% (20/24) of patients received carboplatin within 3 months of orchidectomy .96% (23/24) received 2 cycles of carboplatin. 84% (20/24) were treated with carboplatin AUC 7.5 and 17% (4/24) received carboplatin AUC 7.

4% (1/24) of patients experienced no acute toxicities with carboplatin.17% (4/24) of patients had gastrointestinal toxicity with grade 1 diarrhoea. 13% (3/24) had grade 1 myelosuppression. 8% (2/24) had fatigue and 4% (1/24) had epididymo-orchitis (Figure 1). In terms of long-term toxicities due to carboplatin, 67% (15/24) were well at follow up. 13% (3/24) had ongoing gastrointestinal toxicity.

8% (2/24) had pulmonary manifestations. One patient had lung nodules which were under surveillance, and images reviewed at MDT were consistent with benign lesions. These have since resolved. One patient had asymptomatic interstitial pulmonary changes on imaging four years from his original diagnosis. These changes have improved on follow up scans.

4% (1/24) had grade two fatigue. 4% (1/24) had erectile dysfunction. 4% (1/24) had a cardiac event. This occurred in the patient who was previously treated with radiation (Figure 2).

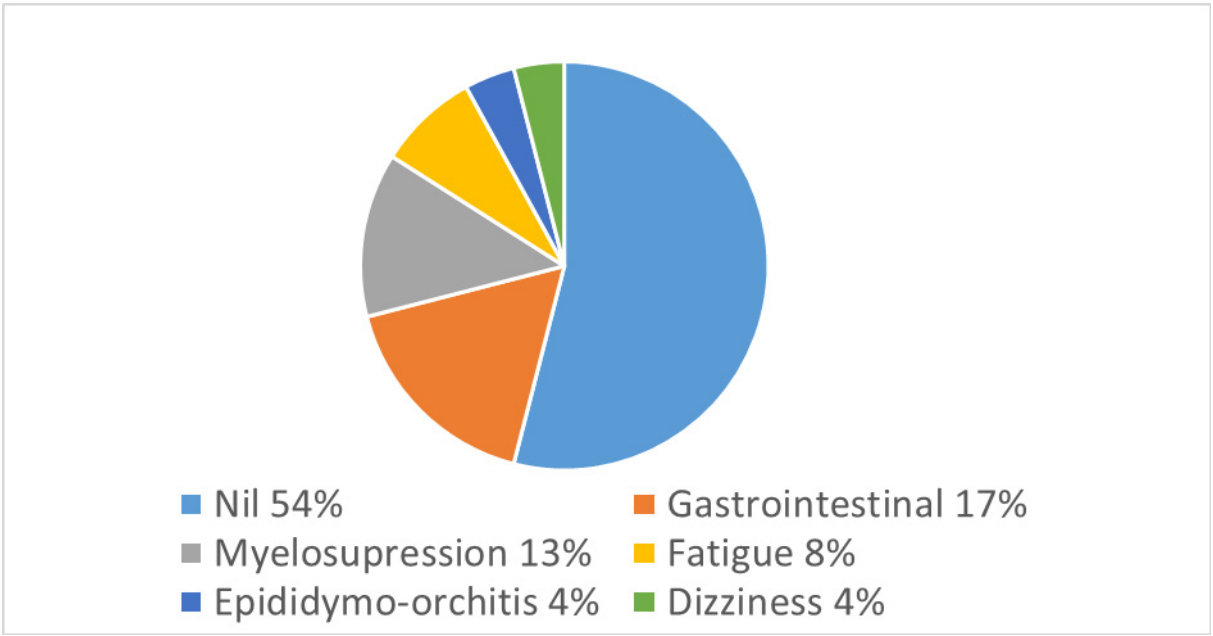

Figure 1. Acute toxicities associated with carboplatin

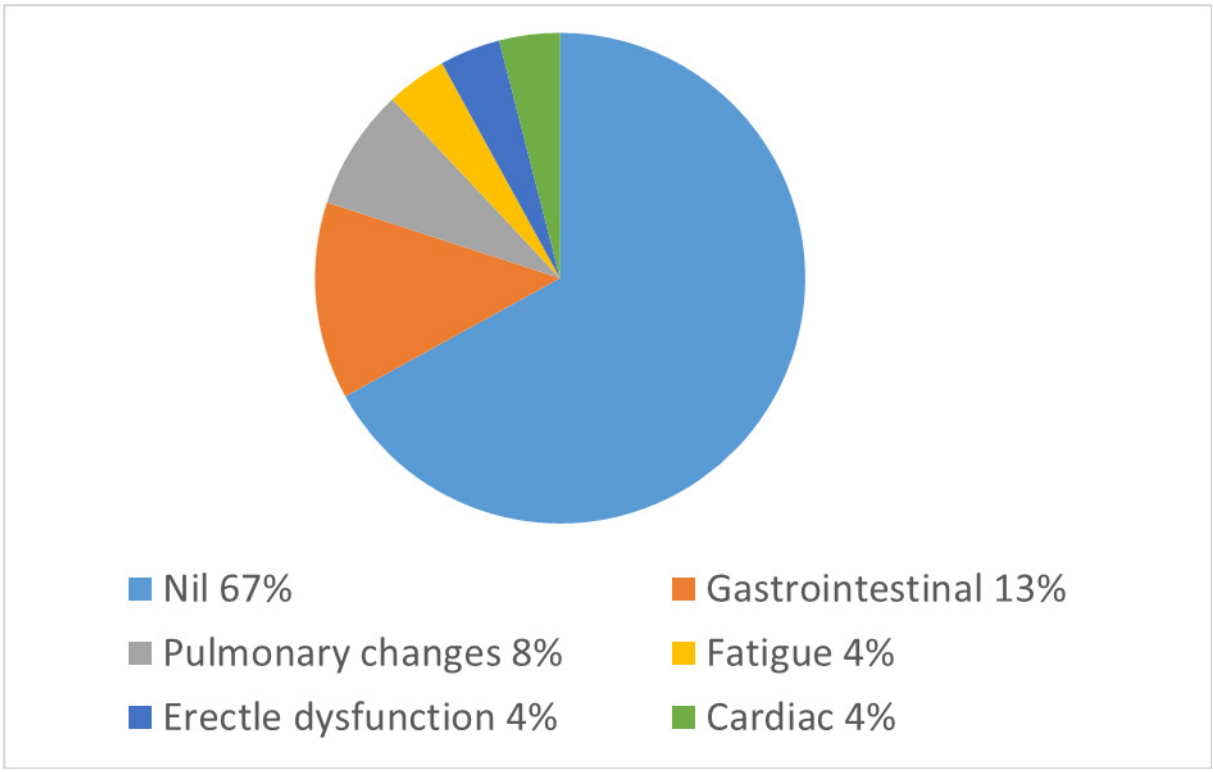

Figure 2. Long-term toxicities of carboplatin

17 % (4/24) had high risk histological features with a tumour size greater than 4 cm and rete testis involvement. Of note histological feature did not correlate with outcomes in this cohort (Table 2).

Table 2. Baseline characteristics

Baseline Characteristics		
Age	20-30 years	25%
	31-40 years	46%
	41-50 years	17%
	51-60 years	12%
Comorbidities	Healthy	84%
	Schizophrenia	4%
	Asthma	4%
	Cerebral Palsy	4%
	HCV	4%

1 patient had recurrent stage 2 disease. His histology at diagnosis revealed a 3.5cm lesion with rete testis involvement. He underwent orchidectomy and had 2 cycles of carboplatin AUC 7.5. He recurred 3 years post his original diagnosis. Radiotherapy was not an option for this patient as he had a horseshoe kidney, so he proceeded to 4 cycles of cisplatin and etoposide.

1 patient had a second malignancy. He was diagnosed with stage 1 seminoma at the age of 50 years and underwent orchidectomy. He had 2 cycles of carboplatin AUC 7.Six years later he was diagnosed with Gleason 3 +3 prostate and underwent radical robotic prostatectomy. He is well at two years follow up.

1 patient, following a diagnosis of stage 1 seminoma, was initially treated with radiation however was stopped due to severe diarrhoea. He proceeded to two cycles of carboplatin AUC 7.5. In long term follow up he has recurrent grade 2 diarrhoea and had a cardiac event aged 48 years, five years post his original diagnosis. He presented with a NSTEMI and requires percutaneous angioplasty and stenting.

4. Discussion

Our study demonstrates the challenges of treating young patients with a highly curable malignancy. In all cases treatment with carboplatin adhered to the current NCCN recommendations regarding dosing and schedules. Overall it was well tolerated with regard to short and long term toxicities. Toxicities when they did occur were expected and known to be side effects of carboplatin. All acute toxicities were manageable however long term gastrointestinal symptoms proved challenging to control. One patient in particular experienced long term grade 2 fatigue which had a significant impact on his ability to work. Though fatigue can be multifactorial in nature it may have been related to previous carboplatin treatment.

One patient unfortunately experienced significant toxicity due to previous radiation treatment. Adjuvant radiotherapy was previously the mainstay of adjuvant treatment for the past fifty years, with long term disease free survival rates of 96% and overall survival rates of 98% (Chung & Warde, 2011). Unfortunately, it has been associated with significant morbidity, including increased cardiovascular disease (Huddart et al., 2003; Zagars et al., 2004) peptic ulcer disease (Fossa, Aass, & Kaalhus, 1989) and a two to three fold risk of secondary malignancies in the irradiation fields (Bokemeyer & Schmoll, 1995; Chao et al., 1995). One patient was initially treated with radiation but due to the acute side effects proceeded to carboplatin therapy. It is possible that the combined use of both agents increased his risk for long term toxicity. Certainly his case demonstrates the concerns surrounding the use of radiation therapy in this setting.

We note that a risk adapted approach using histologic features to predict outcomes and overall survival is not recommended by the NCCN. In our study tumour size or rete testis involvement did not correlate with risk of relapse or overall survival. 25% of our patients had high risk features with tumour size>4cm and associated rete testis involvement. However limitations of this data are the need for longer term follow up to more accurately assess outcomes.

Surveillance is recommended as a reasonable first line option for patients with stage 1 seminoma. The risk of relapse is 20% at 5 years and requires a regular and prolonged follow up schedule. Surveillance is advantageous in avoiding treatment however there is an associated 20% risk of relapse (Oliver et al., 2005) as well as the implications of the risk regarding cumulative radiation exposure due to multiple CT imaging. When relapse does occur it may not be associated with a rise in serum tumour markers, thus there is a reliance on CT surveillance imaging. Relapses often occur late after treatment with only a 6.6% occurrence rate after 5 years (Groll et al., 2007). This necessitates multiple, long term surveillance abdominal and pelvic CT as per NCCN guidelines, resulting in high radiation exposure in such a young cohort. Analysis of a single CT scan of the chest, abdomen and pelvis equates to 19 mSv to the stomach, 20mSv to the bladder and lung (Chung et al., 2010). The lifetime risk of secondary malignancy associated with pre-treatment CT, followed by three more annual CT scans for an 18 yr old male is 0.64% (Chung et al., 2010). With NCCN guidelines, patients could have nine CT abdomen/ pelvis by year five (Mead et al., 2011).

Compliance is a prerequisite to ensure success with this surveillance protocol. The prospect of prolonged surveillance schedules and increasing associated cost can lead to patients to consider carboplatin which requires a less intensive follow up regimen. Many patients find the practical and psychological impact of on-going surveillance difficult. As a young and mobile population the inflexibility of follow up can prove challenging. The Swedish and Norwegian Testicular Cancer Group produces a study looking at patient perspectives to treatment options for stage 1 seminoma. 50% of patients chose adjuvant carboplatin over surveillance alternative showing a preference to avoid psychological stress associated with surveillance protocols and from awaiting a recurrence (Kollmannsberger et al., 2014).

Adjuvant carboplatin represents an alternative therapeutic option for stage one seminoma. Two cycles of carboplatin appears to be more effective than one (Kollmannsberger et al., 2015). Retrospective analysis on long term outcomes with adjuvant carboplatin shows comparable overall cancer specific survival of 99.8% and non-inferiority of carboplatin compared with radiation therapy in terms of relapse rate (Dieckmann et al., 2000). Adjuvant carboplatin with two cycles of treatment has the additional advantage over radiotherapy in reducing incidence of contra-lateral testicular cancer of 0.3% versus 1% in the first four years (Oliver et al., 2011).

In this study carboplatin demonstrated good tolerability in both the short and long term sequelae, with low risk of relapse. Adjuvant carboplatin allows for reductions in frequency of follow up and post treatment imaging (Mead

et al., 2011) which may have a positive psychological impact on patients and provide an alternative management option for patients who will be unable to comply with regular follow up.

The limitations of this study are small number of patients included and the need for longer follow up. However as there is limited Irish data with respect to testicular cancer in the literature this study provides a unique insight into a single centre's experience of managing stage one seminomas.

In conclusion, surveillance is the preferred treatment option for patients with stage one seminomatous germ cell tumours however carboplatin is a safe and well tolerated alternative to active surveillance in a selected group of patients who may have difficulty adhering to recommended surveillance schedules.

Competing Interests

The Authors declare they have no competing interests and all research was carried out within local and national ethical policy guidelines.

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