Pediatr Nephrol (2012) 27:911–916
DOI 10.1007/s00467-011-1998-3

EDUCATIONAL REVIEW

Renal tumours: long-term outcome

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Received: 1 June 2011 / Revised: 21 July 2011 / Accepted: 27 July 2011 / Published online: 27 September 2011

Abstract Childhood cancer is rare, with an incidence of 100 new cases per million children and with renal tumours contributing 7% of cases. The introduction of multimodality treatment, surgery, radiotherapy and chemotherapy, has led to an exponential increase in the 5-year survival rate to >80%. However, this successful treatment has led to the development of late adverse effects. These treatment-related effects can cause premature deaths and increased morbidity compared with patients' peers. Radiation causes damage to tissue and organs within the radiation field, affecting growth and function, and is largely responsible for the leading cause of death, namely, second malignant neoplasms. Another important late effect is cardiac dysfunction due to anthracycline use with or without cardiac radiation. In addition, a few patients have genetic abnormalities predisposing to Wilms tumour development, which result in renal dysfunction in the long term and may be exacerbated by cancer treatment regimens. Awareness of late consequences of cancer treatment is important, as early recognition can improve outcome. When presented with a patient with a history of renal tumours, it is vital to enquire about previous treatment to understand whether it is relevant to the presenting problem.

Keywords Childhood · Renal cancer · Late effects · Survivorship

Introduction

Childhood cancer is rare, with an incidence of 100 new cases per million children and with renal tumours contributing 7% of cases: approximately 100 new cases per year. There are several different types of renal tumours diagnosed during childhood, both benign (mesoblastic nephroma) and malignant [Wilms tumour (WT), clear-cell sarcoma of the kidney, renal rhabdoid, renal-cell carcinoma]. By far the commonest is WT (nephroblastoma) at 85%. Therefore, the majority of long-term follow-up studies feature WT survivors. Treating renal tumours has been highly successful since the introduction of multimodality treatment, with a 5-year survival rate that has increased dramatically over the last three decades from 25% in the prechemotherapy era of the late 1960s and early 1970s, to 90% in the 1990s [1]. Treatment, by design, is cytotoxic and at present is unfocused, so that damage occurs to both cancer cells and normal tissue. The extent of the damage depends on many factors, including patient demographics, genetic factors and treatment modalities and doses required to cure the cancer. The majority of renal tumours occur in young children with WT presenting at a mean age of 3 years. These young patients are highly vulnerable to tissue damage, as the normal growth and development may be affected.

The improving survival rate extending over three decades has enabled good long-term outcome studies to be conducted, providing valuable information to inform follow-up and to improve health status for future patients. This information on treatment-related late effects comes from a variety of studies, including large epidemiological (population/multicentre) and single/multicentre studies. The use of multimodality options has been incorporated into the regimens since the 1980s and consists of surgery, chemotherapy and radiotherapy, with intensity depending on histological diagnosis, disease extent and treatment era [2]. Commonly used drugs are vincristine, actinomycin D, anthracyclines (doxorubicin) and alkylating agents (cyclophosphamide, ifosphamide). More recent protocols incorporate carboplatin and etoposide in high-risk patients. Radiotherapy is prescribed if the disease is outside the resected kidney or there is

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metastatic disease, which is usually confined to the lungs. The total radiation dose and fractionation (daily dose) has changed over the years in an attempt to reduce late effects. Lower total radiation dose given in smaller fractions is beneficial. Surgery generally comprises total nephrectomy, but there is international debate about the value of partial nephrectomy. In bilateral disease or in patients with a predisposition syndrome and at increased risk of developing metachronous tumours, an attempt is made to preserve renal tissue by performing partial nephrectomy.

In this review, we address the major late consequences that occur in survivors of childhood renal tumours, including late mortality, cardiovascular, renal, reproductive function and development of second malignant neoplasms (SMN). Late effects of treatment are defined as clinical or subclinical consequences that persist or appear >5 years after diagnosis.

Late mortality (mortality occurring >5 years from diagnosis)

Mortality studies are robust and largely predate comprehensive morbidity studies. They lead the way to understanding the late effects of cancer treatment, and for this reason, they are discussed first. Three large epidemiological studies have been published in the last few years. The multicentre American Childhood Cancer Survivors Study (CCSS), the National Wilms Tumor Study Group (based in North America) with patient overlap with CCSS and the population-based British Childhood Cancer Survivors Study (BCCSS), all of which assessed causes of death in patients who had survived 5 years from their cancer diagnosis [3–5]. These studies showed that although long-term outcome is excellent, renal cancer survivors are at risk of premature death. Mortality studies in the UK and USA identified an overall standardised mortality ratio of 5.8–4.9 in patients treated from 1940 to 1991 and 1969 to 1995, respectively [3, 5]. Early deaths (<5 years from diagnosis) are mainly due to disease relapse compared with late mortality, for which studies identify a crossover of causes, with fewer deaths due to disease recurrence and more due to treatment-related causes. Over time from diagnosis, the risk of premature death fell from a 13-fold at 5–10 years from diagnosis to 5-fold at 30 years compared with age- and sex-matched peers in the general population [4]. Encouragingly, there is a trend that more contemporary patients may be at less risk of premature death [3]. Analysis of the causes of late deaths across all reports identified SMN as the leading cause, followed by cardiac and pulmonary disease [3–5].

Overall late morbidity

Following on from the mortality studies, two studies reported on overall morbidity: a patient questionnaire study from the American CCSS [6] assessed 1,256 WT survivors diagnosed between1970 and 1986, and Greenan et al. published a smaller study using clinically obtained data in 189 survivors from a single centre who were diagnosed between 1966 and 2004 [7]. In the latter study, 29% of survivors had no adverse effects, and 12% demonstrated a high or severe burden of adverse effects. The authors emphasised the increased risk of cardiovascular problems after anthracyclines and thoracic and/or abdominal radiation, with relative risks (RR) of 3.55 [95% confidence interval (CI) 1.52–8.20] and 2.36 (95% CI 1.69–3.29), respectively. The large multicentre study reported a cumulative incidence of severe chronic health conditions of 24% at 25 years. Interestingly, compared with sibling controls, there was no difference in mental health status, socioeconomic outcome and health-care use [6].

Cardiotoxicity

Cardiotoxicity is a leading cause of morbidity due to the use of anthracyclines (doxorubicin is commonly used) and radiation when the radiation field involves the heart. Anthracyclines were added to the treatment regimen in the late 1970s, with the immediate benefit of increasing survival in high-stage disease. Since their early use, there has been an appreciation of their preferential myocyte toxicity causing cardiomyopathy. Clinical heart failure is the most common presentation, which may occur acutely or many years from the completion of treatment [8, 9]. In a single-centre British study, cardiac function was evaluated 1.0–18.8 (mean 7.1) years after completion of treatment in 97 children whose therapy for WT included an anthracycline (mean cumulative dose 303 mg/m^2) [10]. Subclinical cardiac abnormalities, identified by detailed echocardiograms, were found in 25% of patients. In multivariate analysis that included cardiac radiation (from lung and left-flank radiation), only increasing cumulative dose and dose intensity were significant risk factors for impaired cardiac function. With longer follow-up, an American study reported that the cumulative risk of clinical congestive heart failure 20 years after diagnosis was 4.4% in relapse-free WT patients whose treatment included anthracyclines with or without cardiac irradiation, and this increased markedly to17.4% in survivors of relapsed WT [11, 12]. A number of studies have highlighted the progressive nature of the damage, with an increasing life-long risk of developing clinical cardiac dysfunction, which may necessitate a cardiac transplant [13–15]. Follow-up involves regular echocardiography, the frequency of which depends upon the possible risk of progressive disease [16].

Renal disease

As expected, there is a degree of renal impairment in survivors of renal cancer, although recent studies are reassuring [17]. Renal function can be affected by all treatment modalities: surgery reducing the renal mass, radiation to the remaining kidney(s) or nephrotoxic chemotherapeutic agents (Ifosphamide, carboplatin), in addition to genetic conditions. Encouragingly, renal disease is not a major issue for uncomplicated unilateral renal tumours. Patients at maximum risk of end-stage renal disease are those with bilateral disease, occurring either synchronously and metachronously or in association with a WT-1 mutation [WT–aniridia syndrome (WAGR), Denys–Drash and the rarer Frasier syndrome] [18]. A study using the National Wilms Tumour Study Group database between 1969 and 1994 identified a cumulative incidence of end-stage renal failure at 20 years in unilateral disease to be 0.6% when there was no evidence of WT-1 mutation or genitourinary anomalies. However, renal failure occurred in 74% of those with accompanying Denys–Drash syndrome, 36% in WAGR patients and 7% in male patients with cryptorchidism or hypospadias. In those with bilateral disease, end-stage renal disease occurred in 12%, with a higher incidence in WAGR patients of 90%, and 20% in males with associated genitourinary anomalies [18]. Interestingly, patients with intralobar nephrogenic rests identified in the healthy part of the kidney but with no known predisposition had a slightly increased risk of renal disease compared with those with healthy kidney surrounding the WT [19].

Survivors of childhood cancer who have undergone nephrectomy or bilateral partial nephrectomy may be at risk of late hyperfiltration injury and/or hypertension. Compensatory hypertrophy of the remaining kidney is a well-documented finding after nephrectomy [20, 21]. Although this adaptation may initially increase glomerular filtration capacity, there may be a later development of glomerulosclerosis [22, 23], and interstitial injury [23] may ultimately lead to renal function deterioration. The prevalence of microalbuminuria, which is indicative of glomerular hyperfiltration, following nephrectomy for WT is less clear and has been reported to range from 5% to 84% [24, 25]. Diastolic hypertension has been reported, although the incidence is variable: from 0–7% [18, 20, 24]. In a large analysis of 1,171 children treated for WT whose blood pressure was measured 5 years after diagnosis, 83 (7%) had a diastolic blood pressure >95th percentile for age [24]. The relative contribution of nephrectomy to this complication was unclear because a substantial proportion of patients with diastolic hypertension had also received abdominal radiotherapy.

Ifosfamide has been used in some protocols for first-line treatment in high-stage disease and in relapse protocols. This alkylating agent is nephrotoxic, causing both tubular (Fanconi's syndrome) and glomerular damage [26, 27]. The risk of developing nephrotoxicity is related to the total cumulative dose of Ifosfamide (>60–100 g/m^2) [25–27] and to patient-related factors such as the presence of a single kidney [28], renal irradiation [29] and young age [30–32]. Clearly, patients with WT are at particular risk. The prognosis of the nephropathy is variable, with some patients no longer requiring electrolyte supplementation and others progressing to renal failure [33]. In tumour relapse, patients can be salvaged with a combination of agents—ifosfamide, carboplatin and etoposide, which is nephrotoxic—and careful monitoring is required [34]. The recommendations for survivor follow-up are regular urinanalysis and blood pressure monitoring, with more intensive follow-up in the at-risk patients [17].

Fertility and pregnancy outcomes

Of great concern to survivors is the issue of fertility and whether their offspring will be affected by their previous treatment. The first-line chemotherapy used, in general, does not affect either ovarian reserve or male fertility. Cyclophosphamide used in high-risk patients may affect sperm count, but it is unlikely to cause ovarian failure [35]. Ifosfamide can affect fertility, but the doses used in the relapse protocols are lower than shown to cause gonadal damage [36]. Abdominal radiation has a more detrimental effect on female reproduction. Radiation to the abdomen usually involves the pelvis, and therefore, the ovaries and uterus may be in the field and at risk of damage. Whole-abdomen radiation usually results in primary ovarian failure or premature menopause. Several studies demonstrated that the offspring of women who received flank radiation for WT were more likely to have a birthweight <2,500 g, prematurity and foetal malposition than were those born to women whose protocol treatment did not include flank irradiation [37–39]. An added complication is the unusual finding that genitourinary anomalies are known to occur in WT patients, including Müllerian duct anomalies, with septate/unicornuate uteri occurring [39, 40]. Nicholson et al. reported uterine abnormalities in 8% (2 of 24) of female WT patients, one of whom had WAGR syndrome [40].

Second malignant neoplasms

The occurrence of second tumours within the cancer population, either benign or malignant, is a well-recognised late sequel of therapy, and WT survivors are no exception. The less serious occurrence of osteochondromas, or benign bone tumours, may be associated with radiation of the epiphysis of growing bone. These tumours can cause pain, affect function and be unsightly, requiring surgical intervention [41–43]. Interestingly, these tumours

have been reported in unirradiated WT patients, some of whom had a family history of multiple exostoses [44, 45]. Patients exposed to radiotherapy, certain chemotherapy agents or with a known familial cancer predisposition syndrome have all been demonstrated to have an increased risk of second cancers. Studies across a number of countries have given a range of cumulative incidence of 0.65–0.8% at 10 years, increasing to 4.8–7.0% at 30 years, with no obvious plateau. Radiation therapy has been consistently shown to be an important contributory factor in the excess risk of subsequent cancers. Breslow et al. reported that 73% of second solid tumours occurred within the radiotherapy field, and they found clear evidence of an increase in the risk of second cancer with increasing doses of radiation [46]. This is supported by Taylor et al., who reported that 35 of 39 solid tumours were within the radiation field and the majority had an estimated radiation dose of >25 Gy [47]. An international analysis of SMN in WT survivors showed a consistent rate across countries [48].

Tumour types vary; they include bone and soft-tissue sarcomas, breast cancer, lymphoma, tumours of the digestive tract and melanoma [46, 47]. Acute leukaemias also occur, particularly in patients treated in the modern era. It has been postulated that this may be due to more intensive chemotherapy regimens [48].

Other late effects

Radiotherapy causes disruption of tissue growth and therefore these young patients, in addition to the main late effects, do exhibit poor development of both muscle and bone within the radiation field. For example, patients who received flank radiation have reduced final height because of poor growth of the irradiated spine, with the degree of shortening depending on the dose and age at treatment. In addition, there is soft-tissue hypoplasia with truncal asymmetry when flank radiation has been given [49, 50]. In the recent BCCSS study, the Physical Component Score (PCS) analysis showed a normal result in the younger age range (16–19 years) but worsened with age so that survivors >35 years showed a significant difference in mean PCS score, with values of −3.0 compared with population norms. Females performed consistently worse than males. Twenty-five percent stated they could not walk a mile, with 9% being unable to walk 100 yards [51]. From a socioeconomic aspect, WT survivors compare well with the general population with comparable educational attainments [51], employment [52] and mental health outcomes [51, 53, 54].

Conclusions

In this review, we addressed the potential late consequences of successful treatment for childhood renal tumours. It is important to view these late consequences within the context of the wider clinical picture. WT treatment has been a success story, and >80% of children diagnosed with WT can look forward to long-term survivorship. The late complications are a consequence of the type and intensity of treatment required, which in turn reflects the nature and extent of the original tumour. The late effects reported here are a reflection of treatments given over many decades, and the next generation of treatment protocols hopefully will cause less problems as international groups design new strategies to try to reduce late sequelae. From a nephrology perspective, the majority of survivors have few renal problems. In the future, genetic research may well identify those at particular risk who will then require specialised nephrology follow-up. For all survivors, there is a need for long-term follow-up programmes to be developed, with individualised follow-up plans designed to optimise the patient's knowledge of long-term risks, in addition to providing specific clinical surveillance to achieve early diagnosis of sequelae and determine effective management [17, 55].

Questions (Answers appear following the reference list)

1. Which treatment modality is responsible for the majority of late effects?
   (a) Surgery
   (b) Radiotherapy
   (c) Alkylating agents
   (d) Anthracyclines
   (e) Carboplatin
2. Which subset of patients are at significant risk of renal failure?
   (a) Unilateral disease with genitourinary abnormalities
   (b) Beckwith–Wiedemann syndrome
   (c) Bilateral disease
   (d) Treatment with anthracyclines
   (e) WAGR patients
3. Which of the following is true about anthracyclines?
   (a) Cause stunted growth
   (b) Late effect is associated with total dose administered
   (c) Cardiotoxicity seen is commonly due to dysrhythmias
   (d) After the initial hit, there is no progression of cardiac disease
4. Which of the following is true about second tumours?
   (a) Always malignant
   (b) Generally occur outside the radiation field
   (c) Occur many decades from the original treatment
   (d) Caused primarily by chemotherapy
5. Which of the following is true about effects on fertility?
   (a) Males are more at risk of infertility than females after treatment for Wilms tumour

(b) Etoposide is the drug commonly associated with infertility
(c) The foetus is at risk of hydramnios
(d) Premature births occur more frequently in patients who have not received radiation
(e) Offspring are generally not at risk of developing WT

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Answers:

1. b
2. e
3. b
4. c
5. e