THERAPY BASED LONG TERM FOLLOW UP

(2nd EDITION, APRIL 2005)

Practice Statement

UNITED KINGDOM CHILDREN'S CANCER STUDY GROUP
LATE EFFECTS GROUP

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Long Term Follow Up Therapy Based Guidelines
(1st Edition) 1995
Edited by GDN Kissen and WHB Wallace

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Contents

Introduction

The intention of this Practice Statement "Therapy Based Long Term Follow Up" (2nd Edition) is to inform and guide all clinicians responsible for the clinical follow up of long term survivors of treatment for childhood malignancy, including survivors of bone marrow transplantation (BMT). The Practice Statement updates and extends the information available in the 1st edition "Long Term Follow Up Therapy Based Guidelines" (1995, ed GDN Kissen, WHB Wallace), which was also produced by the UKCCSG Late Effects Group (LEG). The Practice Statement incorporates four new sections *(Recipients of blood products, Neurological, Spine, Absent or dysfunctional spleen)* and 3 new appendices (two that draw together the many aspects of follow-up required for *Survivors of CNS tumours* and *Survivors of BMT*, and one that summarises recommendations for *Immunisation after completion of treatment*).

The format is similar to that of the 1st edition "Long Term Follow Up Therapy Based Guidelines" (1995). The recommendations for follow-up assessments and investigations are based on knowledge of the treatment that the individual patient has received. This information allows the clinician to anticipate the likely late adverse effects that need to be considered, evaluated and sometimes treated, and to design a suitable follow-up plan. This plan will incorporate appropriate initial clinical assessment and investigations as well as further actions (eg subspecialist referral), but the recommendations are not intended to be exhaustive, nor to provide specialist guidance concerning the subsequent management of established toxicity. Since there is usually very little clear evidence concerning the optimum frequency of long term follow up evaluation, this will depend to some extent on clinical and local organisational factors. Many patients will be reviewed in specific Long Term Follow Up clinics at infrequent but regular intervals (eg annually, or in some selected cases, every two years), and this is acknowledged by the statement "at Long Term Follow Up clinic" in the following sections. Therefore, few defined intervals of evaluation are suggested in this document, and those that are specified should be regarded as pragmatic suggestions based on clinical experience and expert opinion, rather than high grade recommendations. Although not explicitly stated, it is expected that paediatric specialists will be consulted when subspecialist referral is required unless patient age (adolescent or young adult) or local circumstances or expertise dictate otherwise. In summary, this Statement aims to help and guide busy clinicians, but not to replace clinical judgement nor to be proscriptive.

Responsibility for the 25 system, organ, tissue or function based sections and the five Appendices has been shared amongst ten current and one former member of LEG and one co-opted contributor from UKCCSG. The contributors for specific sections were chosen in the light of their specific research and clinical interests and expertise in the relevant topics. In producing their recommendations for follow up, the contributors have utilised many sources of information, principally their specialist knowledge of the published literature, augmented by formal literature searches. However, there are relatively little published data available concerning many of the late adverse effects of treatment, and in these instances, the contributions in this Statement also draw on information from expert committee reports and opinions, and the clinical experience and practice of respected authorities. In view of the paucity of controlled studies, formal critical appraisal has not been performed except for those contributions cross-referenced to the Scottish Intercollegiate Guidelines Network (SIGN) document "Long term follow up of survivors of childhood cancer".

Wherever possible, appropriate references have been included to indicate the basis for the recommendations in the Practice Statement. Those references cited offer information concerning the nature, and risk factors for the development, of the late adverse effects of treatment, and their investigation and management. Review articles are referenced in individual sections where they provide useful perspective. The reference lists provided are not intended to be complete, but rather to be representative.

Introduction to Long Term Follow Up Therapy Based guidelines, 1995
United Kingdom Children's Cancer Study Group Late Effects Group
ed GDN Kissen, WHB Wallace

While the early follow-up of children treated for cancer is primarily to detect relapse or recurrence, the balance changes for the long term survivor, where it becomes important to identify the late effects of therapy.

This is important because the late effects may be amenable to treatment and may have significant implications for later life, for example fertility, employment and physical activity. A knowledge of the incidence and consequences of these late effects is essential to make balanced decisions on the benefits and risks of the treatment modalities currently available. The relevance of this is emphasised by the fact that almost 1 in 1,000 of our young adult population is now a survivor of childhood cancer.

The risks of late effects are directly related to the treatment received. Almost all treatment regimens have changed over the years and therefore these guidelines are therapy based. They are intended to provide guidance for the surveillance of survivors at least three years off therapy. They do not form a screening programme.

It is important to remember that the risks of dying from a treatment related death remain lower, at around 2%, than the risk of dying from recurrent disease, at around 8%, in the subsequent 10 years for those surviving 5 years after diagnosis. The risks of second malignancy are between 2% (for acute lymphoblastic leukaemia) and 8% (for Hodgkin's Disease).

The protocols should be utilised in the out-patient clinic to prompt appropriate surveillance. Each patient should be involved in this part of their care and should be informed in a way that is appropriate to their age, maturity and understanding. The right to a confidential consultation should be recognised and respected.

How to use this practice statement

1. Summarise the treatment received under the headings:
   - Chemotherapy
   - Radiotherapy
   - Surgery

A summary sheet is provided which can be photocopied and retained in the notes (page 57).

2. Work through the *Treatment / Potential late adverse effect* lists (pages 6 to 10) and select the appropriate *Follow -up protocol* by number.

All patients require protocols no's 1 and 2; nearly all will need no 3.

3. A summary list of the *Follow-up protocols* is provided with tick boxes to indicate those relevant (see page 56). This list may be photocopied and retained in the patient notes.

4. Follow the recommendations for long-term patient follow-up and management as detailed by the relevant *Follow-up protocols*.

5. A list of possible investigations is also provided (see page 58) and may be photocopied and retained with the treatment summary and protocol list in the clinical notes.

6. The presence of a "?" indicates an element of doubt about the association between the potential problem and the treatment.

The guidelines are intended to be retained on the desk for reference. Further updates will be added to the web version www.ukccsg.org on a regular basis, and it is hoped that updated hard copy editions will be provided when appropriate.

Potential late adverse effects - all patients

Potential late adverse effect	Protocol No.
Impaired quality of life	1
Secondary malignancy	2
Transfusion-associated complications	3

Potential late adverse effects of chemotherapy

Drug received	Potential late adverse effect	Protocol
All chemotherapy	Impaired quality of life	1
	Secondary malignancy	2
	Transfusion-associated complications	3
	Dental caries	8
	Pigmented skin lesions	23
	Impaired immunity against vaccine-preventable infections	E
Actinomycin D	Hepatic dysfunction	18
Amsacrine	Cardiac dysfunction	14
Asparaginase	No specific late adverse effect known	
BCNU (carmustine)	Secondary leukaemia	2
	Gonadal dysfunction	11, 12
	Respiratory dysfunction	15
	Renal dysfunction	20
Bleomycin	Respiratory dysfunction	15
Busulphan	Secondary leukaemia	2
	Gonadal dysfunction	11, 12
	Respiratory dysfunction	15
	Hepatic dysfunction	18
Carboplatin	Auditory dysfunction	7
	Renal dysfunction	20
CCNU (lomustine)	Secondary leukaemia	2
	Gonadal dysfunction	11, 12
	Respiratory dysfunction	15
	Renal dysfunction	20
Chlorambucil	Secondary leukaemia	2
	Gonadal dysfunction	11, 12
Cisplatin	Peripheral neuropathy	4
	Auditory dysfunction	7
	Gonadal dysfunction	11, 12
	Renal dysfunction	20
Cyclophosphamide	Secondary leukaemia	2
	Gonadal dysfunction	11, 12
	?Cardiac dysfunction	14
	Bladder dysfunction	21
Cytarabine	Neuropsychological dysfunction	5
	Gonadal dysfunction	11, 12
Dacarbazine	Secondary leukaemia	2
	Gonadal dysfunction	11, 12
Daunorubicin	Cardiac dysfunction	14
Doxorubicin	Cardiac dysfunction	14
Epirubicin	Cardiac dysfunction	14
Estramustine	Secondary leukaemia	2
	Gonadal dysfunction	11, 12

Etoposide (VP-16)	Secondary leukaemia	2
Fludarabine	No specific late adverse effect known	
Hydroxyurea	No specific late adverse effect known	
Idarubicin	Cardiac dysfunction	14
Ifosfamide	Secondary leukaemia Gonadal dysfunction Renal dysfunction Bladder dysfunction ?Reduced bone mineral density	2 11, 12 20 21 22
Melphalan	Secondary leukaemia Gonadal dysfunction Renal dysfunction	2 11, 12 20
Mercaptopurine	No specific late adverse effect known	
Methotrexate	Neuropsychological dysfunction Hepatic dysfunction Renal dysfunction ?Reduced bone mineral density	5 18 20 22
Methyl-CCNU (semustine)	Secondary leukaemia Gonadal dysfunction Renal dysfunction	2 11, 12 20
Mitozantrone	Cardiac dysfunction	14
Mustine	Secondary leukaemia Gonadal dysfunction	2 11, 12
Nitrogen mustard	Secondary leukaemia Gonadal dysfunction	2 11, 12
Procarbazine	Secondary leukaemia Gonadal dysfunction	2 11, 12
Steroids	Visual dysfunction (cataract) Reduced bone mineral density	6 22
Teniposide (VM-26)	Secondary leukaemia	2
Thalidomide	Peripheral neuropathy	4
Thioguanine	Hepatic toxicity	18
Thiotepa	Secondary leukaemia Gonadal dysfunction	2 11, 12
Vinblastine	No specific late adverse effect known	
Vincristine	Peripheral neuropathy	4

NB This Table is not intended to be inclusive of all late adverse effects of chemotherapy conditioning for BMT – see Appendix B

Potential late adverse effects of radiotherapy

Site	Potential late adverse effect	Protocol
Any site	Secondary malignancy	2
Central nervous system	Neuropsychological dysfunction	5
	Hypothalamic / pituitary dysfunction	9
	Reduced bone mineral density	22
Spinal (check extent of radiotherapy field)	Thyroid dysfunction	10
	Adverse pregnancy outcome	11
	Gonadal dysfunction	11, 12
	Scoliosis, kyphosis	13
	Cardiac dysfunction	14
	Respiratory dysfunction	15
	Breast hypoplasia, malignancy, impaired lactation	16
	Renal dysfunction	20
	Bladder fibrosis, haemorrhagic cystitis	21
	Reduced bone mineral density	22
Ear*	Enhancement of hearing loss	7
Eye*	Cataract	6
	Lacrimal gland dysfunction	6
Mouth, jaw*	Dental caries	8
	Dental hypoplasia	8
	Salivary gland dysfunction	8
Neck (including spinal)	Thyroid dysfunction, nodules, malignancy	10
Thoracic (including spinal)	Cardiovascular disease	14
	Respiratory dysfunction	15
	Breast hypoplasia, malignancy, impaired lactation	16
Abdominal	Adverse pregnancy outcome	11
	Gastrointestinal dysfunction, diarrhoea	17
	Gastrointestinal fibrosis, stricture	17
	Hepatic dysfunction	18
	Hepatic fibrosis, cirrhosis	18
	Splenic dysfunction	19
	Renal hypoplasia	20
	Glomerular dysfunction	20
	Proteinuria	20
	Hypertension	20
Pelvic	Adverse pregnancy outcome	11
	Uterine hypoplasia, fibrosis, reduced elasticity	11
	Bladder fibrosis, haemorrhagic cystitis	21
	Avascular necrosis	22
Gonads*	Adverse pregnancy outcome	11
	Hypogonadism	11, 12, C
	Impaired fertility	11, 12, D
Bone	Avascular necrosis	22
	Fracture	22, 24
	Hypoplasia, deformity	24
Skin, hair	Pigmented skin lesions	23
	Hypoplasia, fibrosis, atrophy, telangiectasia	23, 24
Soft tissue	Hypoplasia, fibrosis, atrophy	24
Any major artery*	Atheroma, stenosis	24
TBI	All of above	1 – 24 B, C, D, E
MIBG	Thyroid dysfunction	10

* any field including this site

NB This Table is not intended to be inclusive of all late adverse effects of radiotherapy conditioning for BMT – see Appendix B

Abbreviations MIBG - ^{131}I-metaiodobenzylguanidine TBI - total body irradiation

Potential late adverse effects of surgery

Site	Potential late adverse effect	Protocol No.
Intracranial	Neuropsychological dysfunction Hypothalamic / pituitary dysfunction Motor / sensory dysfunction	5 9 25
Orbital	Dysfunction, deformity	25
Neck	Thyroid dysfunction	10
Spine	Deformity, scoliosis, kyphosis	13
Pulmonary	Dysfunction	15
Gastrointestinal	Dysfunction, malabsorption, stenosis, obstruction (site and length dependent)	17
Hepatic	Dysfunction	18
Splenectomy	Increased risk of encapsulated bacterial infection	19
Renal	Glomerular dysfunction Hypertension	20 20
Lower urinary tract	Dysfunction	21
Pelvic	Gonadal Sexual dysfunction (eg impotence)	11, 12 11, 12
Ostomy	Dysfunction	25
Limb endoprosthesis	Dysfunction Loosening Infection Asymmetrical growth	25 25 25 25
Amputation	Dysfunction Prosthesis	25 25
Mutilating surgery	Dysfunction Deformity	25 25

1. Quality of life

HISTORY

Enquire at Long Term Follow Up clinic re:

1) Relationships - friends, family
2) Emotional function, including anxiety and depression
3) Leisure activities
4) Concerns re physical appearance and function
5) School attendance and performance
6) Plans for the future, eg after school
7) Work performance, including employment
8) Sexual function
9) Insurance and related issues
10) Compliance with treatment (where relevant)

RISK FACTORS

- Relevant for all survivors

ADVISE ON

1) Lifestyle
2) Risk behaviour, including smoking and sunbathing
3) Exercise, diet - including implications for weight and bone density

INTERVENTION

1) Discuss and hand out "After Cure"

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Reviews

1) Eiser C. Practitioner review: Long term consequences of childhood cancer. *J Child Psychol Psychiatry* 1998; **39**: 621-633.
2) Eiser C, Hill, JJ, Vance YH. Examining the psychological consequences of surviving childhood cancer: systematic review as a research method in pediatric psychology. *J Pediatr Psychol* 2000; **25**: 449-460.

Specific

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2. Secondary malignancy

ALL PATIENTS

1) Patient education re risks of secondary malignancy and importance of prompt reporting of new symptoms or masses
2) Detailed history, including family history
3) Careful clinical examination (particularly of the radiotherapy field) at Long Term Follow Up clinic visits; more frequent examination may be needed in response to new or suspicious symptoms / signs
4) Advise on reduction of risk behaviour, especially smoking and sunbathing

PATIENTS WITH A HISTORY OF A FAMILIAL CANCER SYNDROME

1) Discuss referral to Clinical Genetics service

POST–PUBERTAL FEMALE PATIENTS EXPOSED TO THORACIC OR MEDIASTINAL RADIOTHERAPY

1) In addition to management in *All Patients* above, see *Breast*

RISK FACTORS

- Radiotherapy – all tissue in radiation fields
- Chemotherapy, particularly:
  - Epipodophyllotoxins
  - Alkylating agents
- Familial cancer syndromes, particularly:
  - Heritable retinoblastoma
  - Li Fraumeni syndrome
  - Neurofibromatosis type 1
  - Fanconi anaemia

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Reviews

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Specific

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5) Neglia JP, Friedman DL, Yasui Y, *et al.* Second malignant neoplasms in five-year survivors of childhood cancer. Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2001; **93**: 618-629.

3. Recipients of blood products

CLINICAL ASSESSMENT

HEPATITIS C

1) All patients transfused prior to September 1991 should already have been counselled and offered HCV screening
2) Patients found to be HCV serology / PCR positive - refer to Infectious Diseases specialist or Hepatologist for further assessment and management

OTHER INFECTIONS

1) Maintain appropriate degree of suspicion of blood product-transmitted viral or prion infection in any transfused patient

NB In the UK, all blood products are tested for HIV, HBV, HCV, CMV. Prior to September 1991, HCV testing was not included.

RISK FACTORS

- Potentially any patient

Highest risk patients
- Multiple blood product transfusions
- Original diagnosis - leukaemia higher risk than solid tumour
- Chronic immunosuppression

PREVENTION OF TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE

1) Survivors of Hodgkin's disease should receive irradiated blood products except in an emergency. No data available regarding duration of risk after completion of treatment.

2) Allogeneic BMT recipients should receive irradiated blood products until no longer considered immunosuppressed.

RISK FACTORS

Highest risk patients
- Hodgkin's disease
- Allogeneic BMT

REFERENCES

Reviews

1) BCSH Blood Transfusion Task Force. Guidelines on gamma irradiation of blood components for the prevention of transfusion- associated graft-versus-host disease. *Transfusion Med* 1996; **6**: 261-271.
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3) Bird SM. Recipients of blood or blood products "at vCJD risk". *Br Med J* 2004; **328**: 118-119.

Specific

1) Dinsmore RE, Straus DJ, Pollack MS, *et al.* Fatal graft versus host disease following blood transfusion in Hodgkin's disease documented by HLA typing. *Blood* 1980: **55**; 831-4.
2) Gibb DM, Neave PE, Tookey PA, *et al.* Active surveillance of hepatitis C infection in the UK & Ireland. *Arch Dis Child* 2000; **82**: 286-291.
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4. Neurological

CENTRAL NERVOUS SYSTEM

See Neuropsychological, Survivors of central nervous system tumours

NB Severe leucoencephalopathy may cause focal motor signs, spasticity, seizures, ataxia and dementia in addition to neuropsychological dysfunction

PERIPHERAL NERVOUS SYSTEM

PATIENTS TREATED WITH CAUSATIVE DRUGS

At Long Term Follow Up clinic:

1) Enquire re symptoms and examine for signs of peripheral neuropathy
   - Cisplatin – predominantly sensory
   - Vincristine – chronic neuropathy rare, but may follow failure of recovery of acute neuropathy – sensorimotor, autonomic, occasionally cranial nerves
2) Consider neurophysiology studies
3) Consider referral to Physiotherapist and / or Occupational Therapist
4) Consider drug treatment for painful neuropathy

RISK FACTORS

- Chemotherapy
  - Cisplatin, especially with higher cumulative dose (>300 mg/m^2)
  - Vincristine, especially in malnourished patients or if concomitant drug treatment that inhibits vincristine metabolism (eg itraconazole)

REFERENCES

Reviews
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2) Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. *N Engl J Med* 2001; **345**: 425-432.

Specific
1) Hansen SW, Helweg-Larsen S, Trojaborg W. Long-term neurotoxicity in patients treated with cisplatin, vinblastine, and bleomycin for metastatic germ cell cancer. *J Clin Oncol* 1989; **7**: 1457-1461.

5. Neuropsychological

HISTORY

1) Document treatment
2) Enquire at Long Term Follow Up clinic re school / work performance:
   - Type of school attended
   - Work performance, including employment
   - Learning or memory problems
   - Physical function, especially balance and coordination
   - Plans for the future
   - Social function

RISK FACTORS

- Relevant for all survivors, but especially
  - CNS tumours
  - ALL treated by CNS radiotherapy or intrathecal chemotherapy
  - BMT recipients (especially those receiving TBI at an early age)
  - Young age at treatment

ADVISE ON:

1) Careers guidance
2) Opportunities on leaving school
3) Remedial education

PSYCHOLOGICAL ASSESSMENT

Indicated when:

1) Parents / school express concern about child's progress, and especially when
2) Questions / concerns raised about transfer to special school or from primary to high school.

Assessment will include:

- Intellect and achievement
- Personal social adjustment
- Function specific tests

INTERVENTION

1) Discuss and hand out "After Cure"
2) Discuss and hand out "Children with a brain tumour in the classroom"

REFERENCES

Reviews

1) Eiser C. Practitioner review: Long term consequences of childhood cancer. *J Child Psychol Psychiatry* 1998; **39**: 621-633.
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4) Christie D, Leiper AD, Chessells JM, Vargha-Khadem F. Intellectual performance after presymptomatic cranial radiotherapy for leukaemia: effects of age and sex. *Arch Dis Child* 1995; **73**: 136-140.

6. Visual

PATIENTS WITH RISK FACTORS

Regularly at Long Term Follow Up clinic, or if new symptoms:

1) Enquire re visual impairment, tear production, dry or painful eye(s); advise patient to report new symptoms promptly
2) Examine for signs of posterior subcapsular cataract or complications of lacrimal gland atrophy (ie corneal ulceration or scarring)

FURTHER ACTION

1) Refer to Ophthalmologist for assessment and management of symptoms and abnormal signs

RISK FACTORS

- Radiotherapy to field including eye / head / face (including TBI)
- Steroids

REFERENCES

Review

1) Gordon KB, Char DH, Sagerman RH. Late effects of radiation on the eye and ocular adnexa. *Int J Radiat Oncol Biol Phys* 1995; **31**: 1123-1139.

Specific

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7. Auditory

PATIENTS WITH RISK FACTORS

Enquire at Long Term Follow Up clinic re auditory symptoms, especially:

1) Hearing acuity
2) Speech development
3) School and social functioning with respect to hearing and speech

INVESTIGATION

On completion of treatment, perform

1) Pure tone audiogram
2) Paediatric ENT / Audiology assessment (infants) – including behavioural audiometry, and rarely, otoacoustic emissions or auditory brainstem responses

MANAGEMENT OF HIGH RISK PATIENTS

1) Symptomatic patients – refer to Paediatric ENT / Audiology, and to Speech Therapy (where appropriate).
2) Infants and pre-school children treated with cisplatin or high-dose carboplatin – consider referral to Paediatric ENT / Audiology.
3) Children with significant hearing impairment - liaise with Education and Community Paediatric services.

RISK FACTORS

- Cisplatin, especially cumulative dose >400 mg/m2
- Carboplatin (ototoxicity uncommon and usually less severe, but may be clinically significant after high-dose carboplatin)

Other risk factors that may cause or increase hearing impairment:

- Prior cranial radiotherapy to field including middle ear (especially posterior fossa) may enhance hearing loss
- Age <5 years at treatment
- Treatment with other ototoxins (eg aminoglycosides)
- Impaired renal function at time of platinum treatment (leading to higher systemic platinum exposure)

REFERENCES

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Specific

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5) Li U, Womer RB, Silber JH. Predicting cisplatin ototoxicity in children: the influence of age and cumulative dose. *Eur J Cancer* 2004; **40**: 2445-2451.

8. Craniofacial / Dental

ALL PATIENTS

1) Regular dental examination

RECIPIENTS OF RADIOTHERAPY TO FIELD INCLUDING JAW / SALIVARY GLANDS

1) **AVOID adrenaline** containing local anaesthetics
2) Refer to Paediatric Orthodontist

RECIPIENTS OF RADIOTHERAPY TO FIELD INCLUDING FACE

1) Consider regular clinical photography to assist in possible later facial reconstruction
2) Refer to Maxillofacial Surgeon during puberty if facial reconstruction is required

NB Mandible more sensitive to radiotherapy than maxilla.

RISK FACTORS

- Cranial / facial radiotherapy (including TBI)
- Chemotherapy
- Treatment at young age

REFERENCES

Review

1) Dahllof G. Craniofacial growth in children treated for malignant diseases. *Acta Odontol Scand* 1998; **56**: 378-382

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9. Hypothalamic pituitary axis

ALL PATIENTS

1) Measure and chart height and weight at least six monthly until growth complete.
2) Measure sitting height at same time as height and weight if possible. Essential for recipients of TBI, craniospinal or abdominal radiotherapy.
3) Pubertal staging at least six monthly. Includes testicular volume assessment using an orchidometer in boys.
4) Regular (consider annually) bone age in recipients of cranial irradiation, TBI, or patients with brain tumours even in absence of radiotherapy.

RISK FACTORS

- Radiotherapy to field including CNS / spine (including TBI)
- Brain tumours even in absence of radiotherapy
- Bone marrow transplantation – recipients of TBI conditioning after previous cranial radiotherapy are at highest risk

REFER FOR ENDOCRINE ASSESSMENT IF:

1) Height velocity <25th percentile
2) Evidence of puberty at less than 9 years (female) / 10 years (male)
3) Radiotherapy dose to HP axis >30 Gy
4) TBI
5) Height <10th percentile
6) Discrepancy between pubertal stage and growth; watch for attenuated pubertal growth spurt

AFTER CRANIAL RT PATIENTS ARE AT RISK OF:

- Growth hormone deficiency (GHD)
- Attenuated pubertal growth spurt
- Early puberty
- Delayed puberty
- Multiple pituitary hormone deficiency; pituitary hormones lost sequentially in order of GH (first and commonest), LH/FSH, ACTH, TSH; risk increases with increasing dose and time from treatment

GROWTH HORMONE DEFICIENCY

- Most children treated with cranial radiotherapy for brain tumours will be GH deficient by 2 years from treatment
- Early diagnosis and treatment is important as response to GH is poorer than in idiopathic GHD especially in children who have received spinal RT
- Risk of GHD at initial presentation in patients with craniopharyngioma
- GHD is a risk factor for reduced bone mineral density
- There is no evidence of an increased risk of relapse or recurrence in children treated with GH
- Cardiac monitoring is important in children who have received anthracyclines and are receiving treatment with GH
- IGF–1 and IGFBP3 should be monitored in patients receiving GH
- At completion of growth, GH should be discontinued and re-evaluation of the hypothalamic pituitary axis undertaken. If GHD meeting the adult criteria is present, consideration should be given to adult GH replacement in discussion with an adult Endocrinologist. There is evidence to suggest that GH replacement is important for maintaining normal bone mineral density and body composition, as well as quality of life and cardiovascular lipid profile, in adult life.

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10. Thyroid

PATIENTS WITH RISK FACTORS

Annually:

1) Measure T_4 and TSH
2) Palpate neck

NB Risk of secondary thyroid malignancy following radiotherapy to field including thyroid is 6-16 times that expected

IF THYROID FUNCTION ABNORMAL

1) Discuss with / refer to Endocrinologist

   Treatment is indicated if:

   - TSH raised (on 2 successive occasions) and T_4 normal - treat with thyroxine in dose that will suppress TSH
   - TSH raised and T_4 low - treat with thyroxine in dose that will suppress TSH and return T_4 to high normal level

NB Risk of malignant change thought to be increased if TSH is elevated

IF PALPATION ABNORMAL

1) Perform ultrasound scan of neck
2) Refer to Endocrinologist

NB Fine needle biopsy by Endocrine Surgeon likely to be needed

RISK FACTORS

- Radiotherapy to field including thyroid (including neck, spine, mantle, mediastinum, TBI)
- MIBG
- Busulphan based conditioning for BMT

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11. Gonadal - female

ALL PATIENTS

1) Pubertal staging six monthly
2 Measure and chart height at least six monthly until normal pubertal growth spurt established
3) When appropriate, enquire re menstrual history and menopausal symptoms (hot flushes, dyspareunia)
4) When appropriate, discuss need for contraception (even in presence of impaired fertility) and possible risk of premature menopause

PRACTICE POINTS

1) Girls treated with cranial irradiation should undergo assessment of pubertal status and growth three to four times a year from the end of treatment
2) Refer to Endocrinologist if there is concern about:
   - Poor growth (see *Hypothalamic Pituitary Axis*)
   - Delayed pubertal development (see *Facts of Puberty*)
   - Risk of hypogonadism
3) Fertility counselling should be provided to survivors of childhood cancer
4) Women who have evidence of impaired fertility should receive specialist assessment as they might benefit from assisted reproductive technology (ART)

RISK FACTORS

- Radiotherapy to field including ovaries / uterus (including TBI, spinal, abdominal, flank)
- Alkylating agents:
  - BCNU
  - Busulphan
  - CCNU
  - Chlorambucil
  - Cyclophosphamide
  - Ifosfamide
  - Melphalan
  - Mustine
  - Nitrogen mustard
  - Thiotepa
- Cisplatin
- Cytarabine
- Dacarbazine
- Procarbazine

SUMMARY OF THE EVIDENCE

- High dose (>24 Gy) radiotherapy to the hypothalamus / pituitary (eg for brain tumours) may result in delayed puberty, whereas lower doses (<24 Gy) are more commonly associated with precocious puberty especially in young girls.
- In the female, chemotherapy and radiotherapy may damage the ovary and hasten oocyte depletion resulting in loss of hormone production, uterine dysfunction and premature menopause.
- Treatment of Hodgkin's disease with chemotherapy alone is less likely to be damaging to reproductive function in girls than in boys.
- Abdominal, pelvic or total body radiotherapy is likely to result in impairment of ovarian function and may affect uterine function as well.
- Uterine distensibility and blood flow are irreversibly affected by high dose pelvic or abdominal radiotherapy in childhood. Non-invasive assessment by ultrasound examination may predict the potential for pregnancy following ovum donation and embryo transfer.
- Most studies are reassuring about female reproductive outcome after chemotherapy alone for childhood cancer except for treatment for Hodgkin's disease with alkylating agents.
- Although reproductive function after chemotherapy is generally preserved, there is increasing evidence that these patients are at risk of premature menopause.
- Female survivors of Wilms' tumours who have been treated with abdominal radiotherapy are at an increased risk for a variety of reproductive problems including fetal loss, early delivery, and birth defects in offspring.
- Flank radiotherapy is associated with low birth weight in subsequent offspring.
- Females successfully treated for childhood acute lymphoblastic leukaemia without TBI / BMT may be at risk of an earlier than average menopause but are likely to have a window of opportunity for fertility. It would seem sensible not to delay starting a family if children are desired. There is no evidence of an increased risk of congenital anomalies in the offspring.
- A radiotherapy field that includes prepubertal breast tissue may result in significant breast hypoplasia and asymmetry, and also is a significant risk factor for the development of breast cancer.

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1) http://www.sign.ac.uk/pdf/sign76.pdf ("Long term follow up of survivors of childhood cancer. A national clinical guideline")

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12. Gonadal - male

ALL PATIENTS

1) Pubertal staging six monthly, including testicular volume by orchidometer
2) Measure and chart height at least six monthly until normal pubertal growth spurt established
3) When appropriate, discuss need for contraception (even in presence of impaired fertility)
4) Semen analysis when appropriate

PRACTICE POINTS

1) Assessment of male pubertal development and fertility should include six monthly assessment of testicular volume using the Prader orchidometer, Tanner staging of secondary sexual development and 6-12 monthly measurement of serum FSH, LH, testosterone, inhibin B (if available) and semen analysis (when appropriate).
2) Refer to Endocrinologist if there is concern about:
   - Poor growth (see *Hypothalamic Pituitary Axis*)
   - Delayed pubertal development (see *Facts of Puberty*)
   - Risk of hypogonadism
3) With modern assisted reproductive technology (ART), in particular intra-cytoplasmic sperm injection (ICSI), a low sperm count should not preclude fertility
4) Fertility counselling should be provided to survivors of childhood cancer
5) Cryopreservation of semen before cytotoxic treatment should be considered for young male patients whose cancer therapy will include potentially gonadotoxic treatments

RISK FACTORS

- Radiotherapy to field including testes (including TBI)
- Alkylating agents:
  - BCNU
  - Busulphan
  - CCNU
  - Chlorambucil
  - Cyclophosphamide
  - Ifosfamide
  - Melphalan
  - Mustine
  - Nitrogen mustard
  - Thiotepa
- Cisplatin
- Cytarabine
- Dacarbazine
- Procarbazine

SUMMARY OF THE EVIDENCE

- There is a large volume of evidence that both prepubertal and postpubertal testes are susceptible to cytotoxic treatment by alkylating agents or radiotherapy to the gonads.
- Sertoli / germ cells are more susceptible than Leydig cells to chemotherapeutic or radiotherapeutic damage.
- Decreased testicular volume (≤10 ml) is associated with impaired spermatogenesis in the postpubertal male. Therefore testicular volume is not a reliable indicator of pubertal progression in this context. Testicular damage is also associated with elevated FSH and reduced serum inhibin B.
- Direct radiotherapy to the testes cause permanently impaired spermatogenesis and Leydig cell dysfunction.
- TBI causes permanently impaired spermatogenesis but has variable effects on Leydig cell function. Most prepubertal boys undergoing BMT with chemotherapy and hyperfractionated TBI can expect to progress normally through puberty.
- There is evidence for impaired spermatogenesis after treatment for childhood cancer but the sperm produced carries as much healthy DNA as sperm produced by the healthy population.

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Guideline

1) http://www.sign.ac.uk/pdf/sign76.pdf ("Long term follow up of survivors of childhood cancer. A national clinical guideline")

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13. Spine

CLINICAL EXAMINATION

Regularly at Long Term Follow Up clinic:

1) Observe for abnormal spinal curvature, particularly during pubertal growth spurt

FURTHER ACTION

1) Refer to Spinal Surgeon early

RISK FACTORS

- Laminectomy - severity associated with percentage and number of facet joints involved
- Other spinal surgery
- Thoracotomy
- Truncal radiotherapy to field including the spine (including craniospinal, thoracic, abdominal, TBI)
- Young age at treatment

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14. Cardiac

ALL PATIENTS

Regularly at Long Term Follow Up clinic:

1) Enquire re:
   - Exercise tolerance
   - Chest pain
   - Palpitations
   - Shortness of breath
2) Measure blood pressure

ALL PATIENTS WHO HAVE RECEIVED ANTHRACYCLINES REQUIRE:

1) Echocardiogram 1-3 months after last dose of anthracycline
2) If normal at this time, repeat echocardiogram 5 yearly from last dose of anthracycline +/- at end of pubertal growth spurt
3) If abnormal at any stage, discuss with Cardiologist

NB Patients who have not had an echocardiogram within the first 6 months after last anthracycline dose should undergo echocardiography 3 yearly if repeatedly normal.

Abnormal echocardiogram defined as shortening fraction ≤28% (Cube method)

RISK FACTORS

- Anthracyclines and related drugs
  - Daunorubicin
  - Doxorubicin
  - Epirubicin
  - Mitozantrone
  - Idarubicin
  - Amsacrine
- ?High dose cyclophosphamide
- Radiotherapy to field including thorax, thoracic spine or mediastinum (including left flank, TBI)

RECIPIENTS OF THORACIC / MEDIASTINAL RADIOTHERAPY ONLY (IE NO CARDIOTOXIC CHEMOTHERAPY)

1) In view of risk of ischaemic heart disease, consider review of other risk factors eg fasting lipid measurement
2) Prompt investigation of cardiac symptoms as clinically indicated

HIGHER RISK PATIENTS WHO MAY WARRANT MORE FREQUENT SURVEILLANCE INCLUDE:

- Patients previously treated for early anthracycline cardiotoxicity
- Total anthracycline dose >250 mg/m^2
- Combination of radiotherapy and anthracycline
- Strenuous exercise eg weightlifting
- Pregnancy - close monitoring **essential**
- Patients on growth hormone therapy
- Patients on sex steroid replacement therapy
- Patients with congenital heart disease

SPECIALIST REFERRAL

1) All patients with an abnormal clinical examination should be referred to a Cardiologist for assessment and advice about further management
2) Patients with abnormal echocardiogram (see above) should be referred to a Cardiologist for assessment and advice about further management
3) All female patients with a risk factor for cardiotoxicity who became pregnant require close liaison with an Obstetrician

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15. Respiratory

ALL PATIENTS

At Long Term Follow Up clinic:

1) History – exercise tolerance, smoking
2) Examination – respiratory system

NB Late respiratory effects appear to be restrictive rather than obstructive (although the latter can be seen after BMT)

PATIENTS WITH RISK FACTORS

1) Perform baseline pulmonary function tests (PFTs) at end of treatment – restrictive abnormality likely
2) If symptomatic or if abnormal PFTs (<2 SD below normal), repeat PFTs after 1 year and / or consider referral to Respiratory specialist
3) Advise against smoking

SPECIFIC ADVICE TO PATIENTS

1) Advise patients and **warn anaesthetists** about previous bleomycin treatment – high inspired oxygen concentration is associated with risk of worsening pulmonary fibrosis
2) Consider pneumococcal immunisation and annual influenza immunisation in patients with established lung disease

RISK FACTORS

- Chemotherapy
  - BCNU – greater risk with younger age (<5 years) and higher cumulative dose
  - CCNU
  - Busulphan
  - ?Bleomycin – little evidence of late toxicity in children
- Radiotherapy – greater risk with younger age, higher dose and larger treatment volume
  - Whole lung
  - Mediastinal
  - Mantle
  - Craniospinal
  - TBI
- Thoracic surgery
- BMT especially after conditioning with busulphan or TBI

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16. Breast Tissue

ALL POST-PUBERTAL FEMALE PATIENTS

1) Patient education re awareness of breast cancer
2) Regular clinical breast examination by appropriate health care professional
3) Regular breast self examination

CHEST WALL RADIATION
HEREDITARY BREAST CANCER FAMILIES
LI-FRAUMENI SYNDROME

1) Clinical breast examination by appropriate health care professional regularly at Long Term Follow Up clinic once patient >10 years from cancer treatment and >25 years age
2) Discuss with local Breast Cancer service re imaging (but at present imaging techniques are unreliable in patients <45 years age)
3) Discuss referral to Cancer Genetics clinic in patients with ?cancer predisposition syndromes

NB Chest wall radiotherapy may compromise lactation

RISK FACTORS

- Radiotherapy to field including chest wall and breast tissue (including spinal, flank, TBI)
- ± Chemotherapy (alkylating agents)
- Familial cancer syndromes

DH DIRECTIVE 11/03*

Recommended imaging surveillance for high risk females (those treated with mediastinal radiotherapy in childhood [<17 years age]).
Surveillance should start at 25 years of age.

AGE	RECOMMENDED SURVEILLANCE	
<25 years	**No imaging**	
25 - 29 years	**Annual MRI,** but if contraindications to MRI, **Annual Ultrasound** (Mammography is not recommended for this age group)	
30-50 years	**Baseline 2 view mammogram.** Women should then be divided into two groups:	
	Predominantly Fatty Breast Tissue (1)	**Dense Breast Tissue (2)**
	Annual 2 view Mammography	**Annual 2 view Mammography plus MRI** unless: i) there are contraindications to MRI ii) patient cannot tolerate MRI iii) patient chooses not to have MRI In any of the above cases patients should be offered **Annual Mammography plus Ultrasound.** If breast tissue becomes predominantly fatty prior to the age of 50 years the patient should move into group (1), ie. **annual 2 view mammography** only.
>50 years	**Three yearly 2 view mammography** within the NHS Breast Cancer Screening Programme (NHSBCS).	

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17. Gastrointestinal

HISTORY AND EXAMINATION

Enquire at Long Term Follow Up clinic re:

1) Swallowing difficulties, especially dysphagia
2) Bowel habit, especially diarrhoea
3) Symptoms / signs of malabsorption
4) Symptoms / signs of intestinal obstruction

RISK FACTORS

- Radiotherapy to field involving gastrointestinal tract
- Gastrointestinal tract surgery

PATIENTS WITH TERMINAL ILEAL RESECTION OR DYSFUNCTION

1) Consider requirement for vitamin B_{12} replacement

REFERENCES

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Specific

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18. Hepatic

CLINICAL EXAMINATION AND INVESTIGATION

1) At end of treatment and regularly in Long Term Follow Up clinic thereafter, examine for hepatosplenomegaly and stigmata of chronic liver disease - if present, perform abdominal ultrasound scan
2) At end of treatment and as clinically indicated in Long Term Follow Up clinic thereafter, measure liver function tests (bilirubin, transaminases, alkaline phosphatase)

FURTHER ACTION

1) If examination and investigation normal, no further action required unless clinically indicated
2) If examination and / or investigation reveal new or significant abnormalities, investigate as appropriate, or discuss with / refer to Gastroenterologist or Hepatologist

RISK FACTORS

- Hepatic surgery
- Radiotherapy to field including liver (including TBI)
- Chemotherapy
  - Actinomycin D
  - Busulphan
  - Methotrexate
  - Thiopurines, especially 6-thioguanine
- Multiple blood product transfusions *(see Recipients of Blood Products)*

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19. Absent or dysfunctional spleen

BEWARE OF INCREASED RISK OF INFECTIONS

1) Encapsulated bacterial infections
2) Travel infections *(see Additional Advice)*

IMMUNISATIONS

All patients should receive:

1) Pneumococcal vaccine – give conjugate vaccine (3 doses if patient <2 years age, 2 doses if ≥2 years old) initially, followed by one dose of polysaccharide vaccine once ≥2 years old
2) Influenza vaccine annually in autumn (to reduce risk of serious secondary bacterial infection)

Ensure that all patients are fully up to date with:

3) Haemophilus influenzae type b (Hib) conjugate vaccine
4) Meningococcal C conjugate vaccine

NB If elective splenectomy is planned, ensure patient is up to date with Hib and meningococcal C conjugate immunisations, and has received pneumococcal immunisation (as above), **as far in advance as possible.** Otherwise, immunise as soon as possible after splenectomy.

ANTIBIOTIC PROPHYLAXIS (ADULT DOSES)

- Phenoxymethylpenicillin (Penicillin V) 500mg twice daily or
- Amoxycillin 250mg twice daily (may offer better protection against Hib in children) or
- Erythromycin 250mg twice daily (in patients allergic to penicillin, but little activity against *Haemophilus influenzae*)

This should be given for life. In addition, patients should be given a short course of amoxycillin to keep at home (and take on holiday) to be used immediately should infective symptoms develop. In such a situation the patient must be advised to seek immediate medical help. Patients not taking regular antibiotic prophylaxis should be advised to do so during periods of travel.

ADDITIONAL ADVICE

- Patients should be strongly advised of the increased risk of severe falciparum malaria and advised against travel to endemic areas. Strict adherence to chemoprophylaxis is essential when travelling in these areas.
- Animal and tick bites can be dangerous.
- Patients should be encouraged to carry a Medic-Alert disc and information regarding their lack of spleen.
- Patients travelling abroad should request medical review of their prophylaxis before travel, and seek medical advice early if they are unwell whilst abroad, since pneumococci may be more resistant to antibiotics in some countries.

RISK FACTORS

- Splenectomy
- Radiotherapy >40 Gy to field including spleen
- TBI
- BMT for sickle cell disease

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20. Renal

ALL PATIENTS WITH RENAL RISK FACTORS — A

Regularly in Long Term Follow Up clinic:

1) Measure BP
2) Perform urinalysis for proteinuria – if positive (≥++), measure urine protein : creatinine concentration in spot urine sample – if >100 mg/mmol, or if >50 mg/mmol for ≥1 year, discuss with / refer to Nephrologist to consider treatment with ACE inhibitor ± angiotensin II blocking agent
3) Monitor growth at least annually until final height
4) Other investigations as in boxes B,C,D,E below

NEPHRECTOMY OR RADIOTHERAPY — B

Investigations

1) Serum U+Es / creatinine every 5 years
2) GFR (accurate technique) only if high creatinine

NB Discuss follow up of bilateral partial nephrectomy patients with Urologist / Nephrologist

CHEMOTHERAPY — C

Investigations

1) Serum U+Es / creatinine
2) GFR (accurate technique) only if high creatinine
3) Tubular function tests as in boxes D,E below

Timing, intervals and further action

- 1-6 months post-treatment – cisplatin, carboplatin, methotrexate, melphalan
- 1 year post-treatment – nitrosoureas, ifosfamide
- If creatinine normal at these times, repeat 5 yearly, measuring GFR only if high creatinine
- If GFR <90 ml/min/1.73m^2, monitor creatinine yearly and repeat GFR as clinically indicated
- If GFR <60 ml/min/1.73m^2, discuss with / refer to Nephrologist

CISPLATIN / CARBOPLATIN (PLATINUM DRUGS) — D

Investigations

1) General investigations and glomerular function tests as in boxes A,C above
2) Serum magnesium and calcium

Timing and intervals

- 1-6 months post-treatment
- If magnesium and calcium normal at this time, repeat 5 yearly
- If magnesium and / or calcium low, repeat as clinically indicated (eg yearly)

Further action

1) Electrolyte supplementation as guided by serum biochemistry

RISK FACTORS

- Nephrectomy
- Radiotherapy to field including kidney (including TBI, spinal)
- Chemotherapy
  - Nitrosoureas (BCNU, CCNU, methylCCNU)
  - Cisplatin, Carboplatin
  - Ifosfamide
  - Methotrexate (high-dose IV)
  - Melphalan

Particular risk factors may include:

- High cumulative dose (>80 g/m^2 ifosfamide, >1200 mg/m^2 methylCCNU, >15-20 Gy radiation to field including kidney)
- High dose rate (>40 mg/m^2/day cisplatin)
- Young age at treatment (?<5 yr for ifosfamide)

Other risk factors that may cause or increase renal impairment include:

- Other nephrotoxins (eg aminoglycosides, amphotericin B, cyclosporin A)
- Pre-existing renal dysfunction
- Urinary tract obstruction

continued...

20. Renal (continued)

IFOSFAMIDE E

History and examination

1) Enquire re polyuria, polydipsia
2) Signs of rickets or acidosis

Investigations

1) General investigations and glomerular function tests as in boxes A,C above
2) Serum bicarbonate, chloride, calcium, phosphate, alkaline phosphatase
3) Calculate renal tubular threshold for phosphate (Tm_p/GFR) (see box below for calculation)
4) Consider X-rays if clinical or biochemical findings suggest rickets

Timing and intervals

- 1 month post-treatment
- 1 year post-treatment
- If bicarbonate, phosphate and Tm_p/GFR normal at 1 year post-treatment, repeat 5 yearly
- If bicarbonate, phosphate and/or Tm_p/GFR low, repeat as clinically indicated (eg 6 monthly)

Further action

1) Electrolyte supplementation as guided by serum biochemistry
2) Discuss with / refer to Nephrologist if evidence of renal bone disease
3) Warn patient and General Practitioner about possible renal glycosuria

Tm_p/GFR = renal tubular threshold for phosphate A low Tm_p/GFR implies impaired tubular reabsorption (ie tubular toxicity).

(mmol/l) = serum phosphate (mmol/l) – $\frac{\text{urine phosphate (mmol/l) x serum creatinine (mmol/l)}}{\text{urine creatinine (mmol/l)}}$

NB Ensure that the urine collection corresponds to timing of blood sample (ie collect next urine passed after blood taken)

Approximate lower limits of normal	<2 year age	1.10 mmol/l
	≥2 - 12 years	1.00 mmol/l
	≥13 years	0.90 mmol/l

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21. Lower urinary tract

HISTORY

Enquire at Long Term Follow Up clinic re urinary symptoms, especially:

1) Bladder instability and / or irritability
2) Haematuria
3) Urinary retention

INVESTIGATION

If symptoms persistent, consider:

1) Urinalysis
2) Urine microscopy / culture (bacterial, also viral if symptoms persistent and unexplained)
3) Regular (yearly) urine cytology and / or imaging investigations if previous or persistent haemorrhagic cystitis, and / or if new symptoms (note increased risk bladder malignancy)
4) Unrelated causes of symptoms (eg calculi)

FURTHER ACTION

1) Rarely, with persistent severe symptoms, discuss with / consider referral to Urologist for possible cystoscopy and / or urodynamic investigations

NB Severe bladder toxicity may lead to chronic renal impairment due to obstructive uropathy

RISK FACTORS

- Radiotherapy, including
  - Abdominal
  - Pelvic
  - Spinal
  - TBI
- Lower urinary tract surgery
- Chemotherapy, most commonly
  - Cyclophosphamide
  - Ifosfamide
- Viral infection (eg papovavirus, CMV, adenovirus), especially in context of:
  - BMT with associated severe immunosuppression

REFERENCES

Review

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Specific

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22. Bone density

HISTORY

Enquire at Long Term Follow Up clinic re:

1) Back pain
2) Fractures

INVESTIGATION

Consider evaluation of bone mineral density by DEXA scan (or less commonly Quantitative CT [QCT] scan) in:

1) BMT recipients
2) Acute lymphoblastic leukamia (ALL) survivors
3) Medulloblastoma survivors
4) History of fracture
5) History of back pain

NB Interpretation of DEXA scanning in children requires correction for size

MANAGEMENT

1) Treatment of osteoporosis should only be undertaken after discussion with a Specialist in Bone Disease.

RISK FACTORS

- Steroids
- Radiotherapy, including
  - TBI
  - Craniospinal
  - Cranial
  - Spinal
- Endocrinopathy especially
  - Growth hormone deficiency
  - Gonadal failure
- Chemotherapy
  - Standard ALL treatment
  - ?Methotrexate
  - ?Ifosfamide

REFERENCES

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23. Skin

PIGMENTED SKIN LESIONS

1) Inspect all pigmented skin lesions regularly at Long Term Follow Up clinic
2) Photograph skin lesions as clinically indicated and refer worrying lesions to Dermatologist
3) Encourage awareness of warning signs:
   - Increase in size
   - Increase in thickness
   - Change in pigmentation
   - Itching
   - Bleeding

OTHER SKIN LESIONS

1) Inspect skin during any follow-up examination and consider chronic changes due to:
   - Drugs, including steroid toxicity, extravasation damage
   - Radiotherapy toxicity – atrophy, fibrosis, telangiectasia, pigmentation abnormalities, alopecia, malignant lesions (melanoma, basal cell carcinoma, squamous cell carcinoma)
   - Infection, especially viral, fungal (superficial)

GENERAL ADVICE

1) Encourage avoidance of and / or protection against excessive sunlight / UV radiation

RISK FACTORS

- All chemotherapy – all skin
- Radiotherapy – skin in field

REFERENCES

Reviews

1) Susser WS, Whitaker-Worth DL, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. *J Am Acad Dermatol* 1999; **40**: 367-398.
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Specific

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24. Skin/bone/artery/soft tissue in radiotherapy field

ANNUALLY:

Enquire / examine / investigate / refer as appropriate	Late adverse effect	Symptoms / signs
Skin, subcutaneous tissue	Atrophy Fibrosis Hypoplasia Telangiectasia Secondary malignancy	 Mass, ulceration
Major artery	Arterial stenosis	Claudication Transient ischaemic attacks
Coronary artery	Coronary artery disease	Angina
Bone, joint, muscle	Fibrosis Hypoplasia Deformity Stiffness Secondary malignancy	 Mass, pain

RISK FACTORS

- Radiotherapy (all fields)

REFERENCES

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Specific

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25. Major surgical procedure, including endoprosthesis

HISTORY AND EXAMINATION

1) Ensure regular follow-up by Surgical team as appropriate in liaison with long-term follow-up by Paediatric Oncology team
2) Enquire re and examine structural and physiological function of:
   - affected organ / anatomical area
   - affected limb / endoprosthesis
3) Enquire re psychological adaptation to major surgery, endoprosthesis

MANAGEMENT

1) Endoprosthesis: inform patient / family / General Practitioner about need for antibiotic prophylaxis for dental (and other bacteraemic) procedures

SURGICAL TEAMS INVOLVED MAY INCLUDE:

- Neurosurgery / spinal surgery
- Ophthalmic / orbital surgery
- Faciomaxillary / head / neck surgery
- ENT surgery
- Dental surgery
- Thoracic surgery (cardiac, pulmonary)
- Abdominal surgery (gastrointestinal, hepatic)
- Genitourinary / pelvic surgery
- Orthopaedic surgery

See also

- *Neuropsychological*
- *Spine*
- *Respiratory*
- *Gastrointestinal*
- *Hepatic*
- *Absent or dysfunctional spleen*
- *Renal*
- *Lower urinary tract*
- *Survivors of central nervous system tumours*

RISK FACTORS

- Major surgical procedure

REFERENCES

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Appendix A

SURVIVORS OF CENTRAL NERVOUS SYSTEM TUMOURS

Survivors of central nervous system (CNS) tumours may experience difficulties resulting from the destructive effect of the tumour (potential sequelae depend upon tumour location) and therapies used to treat it (neurosurgery, radiotherapy and chemotherapy).

The functional complexity of the CNS, and the susceptibility of the developing brain to injury, result in special requirements for surveillance following treatment. Documentation of specific sequelae of treatment is not enough. Deficits in educational attainment, social competence and behaviour can not be predicted solely by documenting the cognitive, sensorimotor, endocrine and emotional impairments. Therefore evaluation of health in these individuals requires exploration of physical, mental and social well-being along with assessment of autonomy.

This Appendix aims to identify some of the common principles in the after-care of individuals treated for CNS tumours and should be used in conjunction with the other sections relating to late adverse effects arising due to radiotherapy and / or specific chemotherapeutic agents.

A. PHYSICAL HEALTH

SEQUELAE	RISK FACTORS	SURVEILLANCE
Dental problems	• Radiotherapy to field including jaw (base of skull, cervical spine)	• Regular dental review See *Craniofacial / Dental*
Hearing loss	• Platinum chemotherapy • +/- Radiotherapy to field including middle ear (especially posterior fossa)	• Enquire re speech and language development See *Auditory*
Neuro-endocrine and growth	• Tumours in area of hypothalamus or pituitary • Cranial radiotherapy	• Regular anthropometric monitoring • Regular endocrinology review • Pituitary function tests See *Hypothalamic Pituitary Axis*
Secondary tumours	• Radiotherapy • Chemotherapy, particularly epipodophyllotoxins and alkylating agents • Pre-disposition syndromes eg neurofibromatosis type I	• High index of suspicion for lesions (especially skin cancers, meningiomas, glial tumours) within radiotherapy fields • Patient education and regular examination of skin lesions (consider photographs of suspicious lesions) See *Secondary Malignancy*
Shunts (blocked or infected)		• Inform patient of potential complications and symptoms
Thyroid function	• Radiotherapy to field including thyroid (base of skull, cervical spine)	• Clinical screening • Annual thyroid function tests See *Thyroid*
Alopecia	• Radiotherapy to field including scalp	• Clinical examination

B. MENTAL HEALTH

SEQUELAE	RISK FACTORS	SURVEILLANCE

Neurocognitive
Behavioural
	• Combination of cranial radiotherapy and chemotherapy
	• Prolonged school absence
	• Prolonged hospitalisation
	• Physical disability:
	  ◦ Short stature
	  ◦ Obesity
	  ◦ Alopecia
	• Endocrinopathies
		• Enquire re:
		  ◦ Schooling and education
		  ◦ Behaviour
		• Consider referral to:
		  ◦ Psychology
		  ◦ Educational Welfare team and Community Child Health services
		  ◦ Young Adult with Disability team
		  ◦ Social Work team
		See *Neuropsychological*

C. SOCIAL AND ACTIVITIES OF DAILY LIVING

SEQUELAE	RISK FACTORS	SURVEILLANCE

Activities of daily living and self-care
Education
Employment
	• Combination of cranial radiotherapy and chemotherapy
	• Neurocognitive or behavioural difficulties
	• Prolonged school absence
	• Prolonged hospitalisation
	• Physical disability:
	  ◦ Impaired mobility
	  ◦ Short stature
	  ◦ Obesity
	  ◦ Seizures
	  ◦ Visual impairment
	  ◦ Auditory impairment
		• Enquire re:
		  ◦ Daily activities
		  ◦ Self-care
		  ◦ Education / employment
		• Consider referral to:
		  ◦ Psychology
		  ◦ Social Work team
		  ◦ Educational Welfare team
		  ◦ Community Child Health services
		  ◦ Young Adult with Disability team

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Appendix B

SURVIVORS OF ALLOGENEIC BONE MARROW TRANSPLANTATION

Long-term survivors of paediatric bone marrow transplantation (BMT) are at high risk of late adverse effects of treatment. This is due in part to the intensive and high dose nature of treatment, often including radiotherapy (RT), received as part of the BMT process, and in part to the fact that many BMTs are performed for poor prognosis disease. Such patients have already received a great deal of treatment before BMT, involving several cytotoxic drugs and frequently RT. Although BMT is felt to offer the best chance of cure in these children and adolescents, it is acknowledged that considerable late toxicity may be inevitable in a relatively high proportion of patients. Therefore, it is important that survivors of BMT undergo follow up in a setting that allows adequate opportunity for careful review of their physical, mental and psychological health, with recognition and appropriate management of any adverse effects. Nearly all of the published literature about the occurrence of late adverse effects after haemopoietic stem cell transplantation describes patients who have received bone marrow as a source of stem cells rather than peripheral blood or umbilical cord blood, but it is likely that the profile of adverse effects will be broadly similar after these newer techniques due to the significant causative role of prior and conditioning treatment toxicity.

Most of the adverse effects of prior and conditioning chemotherapy and RT in paediatric BMT recipients are the same as those seen in children receiving the same treatment in the non-BMT setting, and are not covered in detail in this section (being cross-referenced instead to other system or site specific sections in this Statement). Nevertheless careful follow up is needed since high treatment doses and / or additive effects may lead to unusual or accentuated toxicity. In addition, survivors of paediatric allogeneic BMT are also at risk of a range of severe and potentially life-threatening manifestations of chronic graft versus host disease (cGvHD), other immune-mediated disturbances (eg haematological cytopenias), and delayed immune reconstitution. A high index of suspicion is needed to enable early detection and optimal management of these complications.

Clinical investigation is complicated by the knowledge that there is a very wide range of severity of clinical abnormalities seen after BMT. Furthermore, it may be unclear whether early diagnosis and perhaps treatment of subclinical toxicity improves the outcome. Unfortunately, the detailed prospective and longitudinal research necessary to understand the true significance of subclinical abnormalities is seldom available.

Table I summarises the characteristics, causes of and higher risk factors for late adverse effects of paediatric BMT, followed by recommendations for clinical assessment, and initial further action that may be required. For each system or site, it is indicated whether routine evaluation (as described in Table I) is required in the absence of overt symptoms, or whether it is only needed in the presence of certain symptoms or signs.

In general, most of the long term follow up evaluations specified in Table I may be carried out in the context of annual reviews, as indicated by the statement "At Long Term Follow Up clinic" in the Frequency column (see footnote d). Table II provides a suggested checklist for quick reference at such reviews. Some units may wish to perform additional investigations in patients receiving BMT for specific or rarer indications. However, an increased frequency of assessment is appropriate in some circumstances, notably during adolescence in view of the need to monitor growth and pubertal development every 3 - 6 months, and also in patients with significant complications (eg active cGvHD) and in patients still within 5 years of transplant. Although the risk of developing a new onset of some late adverse effects decreases with very long term follow up (eg in TBI recipients, the chance of developing primary hypothyroidism for the first time diminishes once more than 10 years post-BMT), this is not true for some other complications (eg secondary malignancies, where the risk continues to increase with time). Nevertheless, once a patient is 10 years post-BMT and at final height, it may be possible to reduce the frequency of follow up to every two years in carefully selected cases. Notwithstanding the above comments, there is very little clear published evidence concerning the optimum frequency of evaluation, and it is recognised that this will vary according to clinical and local organisational factors. Therefore, few defined intervals of evaluation are suggested in Table I, and those that are specified should be regarded as pragmatic suggestions based on clinical experience and expert opinion, rather than high grade recommendations.

As for the Practice Statement as a whole, the information in both Tables is intended to help and guide busy clinicians, but not to replace clinical judgement nor to be proscriptive.

TABLE 1 - LATE ADVERSE EFFECTS OF BONE MARROW TRANSPLANTATION

SYSTEM • OUTCOMES	CAUSES [a] HIGHER RISK FACTORS [b]	CLINICAL EVALUATION [c] FREQUENCY OF FOLLOW UP [c,d,e]	FURTHER ACTION [c,f]
Quality of Life Functional impairment • Family, social • Emotional, relationships • Education, employment • Sexual relationships	• Any treatment	Routine evaluation needed even in absence of overt symptoms See *Quality of Life*	See *Quality of Life*
	• Chronic complications, especially cGvHD	At Long Term Follow Up clinic	
Secondary Malignancy • Solid tumours – especially brain, thyroid, oral / salivary gland, skin; typically later onset (median 4-8 yrs post-BMT) • AML / MDS – predominantly after autologous BMT, very rare in children; usually earlier onset (median 2.5 yrs post-BMT)	• Radiotherapy (RT), including TBI (➔ solid tumours) • Chemotherapy, particularly alkylating agents and topoisomerase II inhibitors (especially epipodophyllotoxins) (➔ AML / MDS) • Immunosuppressive treatment • Familial cancer predisposition syndromes, including Fanconi anaemia	Routine evaluation needed even in absence of overt symptoms See *Secondary Malignancy*	See *Secondary Malignancy*
	• Young age • Cranial / craniospinal RT • High RT dose • cGvHD	At Long Term Follow Up clinic	
Haematology • Immune-mediated cytopenia	• Any allogeneic BMT	Routine evaluation needed even in absence of overt symptoms 1) Symptoms and signs of bone marrow dysfunction 2) FBC	1) Further investigation as appropriate 2) Consider immunosuppression (eg steroids) and / or immunomodulation (eg IVIg)
	• cGvHD	At Long Term Follow Up clinic	
Immunology • Delayed immune reconstitution ➔ increased risk of infection • Auto-immune disease (often associated with cGvHD) - hypo- and hyperthyroidism, myasthenia gravis, diabetes, hepatitis	• Any allogeneic BMT • Prolonged immunosuppression	Routine evaluation may be needed even in absence of overt symptoms 1) Discuss risk, advise about appropriate responses to symptoms of infection 2) Immune function tests – immunoglobulins, lymphocyte subsets (especially CD4) as clinically indicated (until evidence of satisfactory recovery) 3) Further investigation may include auto-antibodies, endocrinefunction tests, LFTs, where appropriate	1) Anti-infective prophylaxis, including IVIg, during risk period; long term antibiotics (eg penicillin V) recommended in TBI recipients 2) Infection surveillance 3) Reimmunisation as appropriate (see also *Appendix E, Immunisation after completion of treatment*) 4) Referral to Immunologist or Endocrinologist as appropriate
	• Mismatched donor BMTs • Unrelated donor BMTs • cGvHD	At Long Term Follow Up clinic	

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
Chronic GvHD (cGvHD) • Secondary malignancy – especially of oral cavity or skin • Haematology – see above • Immunology – see above • Visual – keratoconjunctivitis sicca • Oral – xerostomia, lichenoid or atrophic lesions • Respiratory – obstructive airways disease • Gastrointestinal – nausea, vomiting, oesophageal stricture, diarrhoea, intestinal or pancreatic malabsorption • Hepatic – cholestatic damage • Renal – proteinuria, nephrotic syndrome • Peripheral nervous system – neuropathy, myasthenia gravis, vasculitic syndromes • Musculoskeletal – polymyositis, sclerodermatous joint contractures • Skin – lichenoid or sclerodermatous lesions • Serosal – effusions (pleural, pericardial, peritoneal) • Adverse effects of immunosuppressive treatment – eg steroids, cyclosporin A	Any allogeneic BMT	Routine evaluation needed even in absence of overt symptoms 1) Thorough history and clinical examination 2) High index of suspicion, especially in higher risk patients	1) Further investigations as clinically indicated 2) Immunosuppressive and / or immunomodulatory treatment as clinically indicated 3) Caution regarding adverse effects of immunosuppressive treatment, especially increased risk of infection (see *Immunology* above) 4) Consider reimmunisation with non-live vaccines in patients not on IVIg, but avoid live vaccines (see also *Appendix E, Immunisation after completion of treatment*) 5) Refer to other specialists eg Respiratory as clinically indicated
	• Mismatched donor BMTs • Unrelated donor BMTs • Older patient age at BMT	At Long Term Follow Up clinic	

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
Visual Anterior segment • Posterior subcapsular cataract • Keratoconjunctivitis sicca → corneal / conjunctival ulceration / scarring Posterior segment • Chorioretinitis	• RT to field including eyes (including TBI) • ?Chemotherapy • Steroids • Infection – chorioretinitis (viral, toxoplasmosis)	Routine evaluation needed even in absence of overt symptoms 1) History and examination – vision, dryness or discomfort of eyes, photophobia 2) High index of suspicion for cGvHD in patients with keratoconjunctivitis sicca – look carefully for other features See also *Visual*	1) Refer to Ophthalmologist for assessment of symptoms or abnormal clinical signs 2) Review immunosuppressive treatment in keratoconjunctivitis sicca associated with cGvHD See also *Visual*
	• High RT dose / dose rate • Unfractionated TBI • Prolonged steroid use (cataract) • cGvHD – associated with kerato-conjunctivitis sicca	At Long Term Follow Up clinic See *Visual*	
Auditory • Sensorineural hearing impairment • Impaired speech development	• Chemotherapy – platinum agents (cisplatin > carboplatin)	Routine evaluation needed even in absence of overt symptoms See *Auditory*	See *Auditory*
	• Younger age increases risk of impaired speech development • Higher platinum dose • RT to field including ears – if given prior to platinum • Other ototoxic drugs - especially aminoglycosides	At Long Term Follow Up clinic See *Auditory*	
Craniofacial / dental, oral Craniofacial / dental • Impaired craniofacial skeletal growth • Dental abnormalities, including root, enamel Oral • Reduced saliva → xerostomia, difficulty in mastication and swallowing • Lichenoid lesions / leukoplakia • Oral / salivary gland tumours	• RT to field including jaw (including TBI, cranial) • Chemotherapy • cGvHD	Routine evaluation needed even in absence of overt symptoms 1) History and examination – suspicious intraoral lesions 2) Educate family re importance of regular dental examination 3) High index of suspicion for cGvHD in patients with suspicious oral lesions – look carefully for other features See also *Craniofacial / Dental*	1) Liaise closely with family and hospital dentists See also *Craniofacial / Dental*
	• Young age at treatment • Prior RT (ie before BMT) • cGvHD **NB** Both TBI and cGvHD may contribute to xerostomia and development of tumours	At Long Term Follow Up clinic See *Craniofacial / Dental*	

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
Endocrine / growth • Pituitary – GH deficiency → growth impairment → short stature, skeletal disproportion, reduced BMD, adult GH deficiency syndrome • Thyroid – hypothyroidism, hyperthyroidism (rare), autoimmune disease, benign and malignant tumours • Adrenal – hypoadrenalism rarely observed unless prolonged steroid treatment • Pancreas - metabolic syndrome (hyperinsulinaemia, impaired glucose tolerance, hyperlipidaemia, ±hypertension, ±obesity), diabetes mellitus	• RT to field including affected gland (TBI, TLI, cranial, craniospinal, thyroid, neck, mantle, mediastinum, ?abdominal [pancreas]) • Chemotherapy, including busulphan and cyclophosphamide • Steroids (growth impairment)	Routine evaluation needed even in absence of overt symptoms Growth See also *Hypothalamic Pituitary Axis* 1) Measure height (including sitting height) and weight, calculate height velocity 2) Measure IGF-1 and bone age in TBI recipients if concern about growth (in liaison with Endocrinologist) Thyroid See also *Thyroid* 1) Measure TFTs (T_4, TSH) 2) Palpate thyroid gland Pancreas 1) Symptoms and signs of pancreatic endocrine dysfunction 2) Perform urinalysis for glycosuria 3) Measure fasting blood glucose, fasting lipids, HbA_{1c} **NB** Consider referral to Endocrinologist in all BMT recipients, but especially those who have received TBI or busulphan-based conditioning	Growth See also *Hypothalamic Pituitary Axis* 1) Refer to Endocrinologist for consideration of dynamic GH testing in TBI recipients with slow growth (height velocity <25th centile) and assessment of requirement for GH treatment Thyroid See also *Thyroid* 1) Discuss with / refer to Endocrinologist re thyroxine treatment if compensated or overt hypothyroidism (on 2 successive TFTs measurements for compensated hypothyroidism) 2) Measure thyroid autoantibodies if TFTs abnormal 3) Perform ultrasound scan of neck if thyroid nodule palpated, and refer to Endocrinologist / Surgeon for fine needle biopsy Pancreas 1) Perform glucose tolerance test if fasting glucose elevated 2) Refer to Endocrinologist for management of diabetes or metabolic syndrome
	• Age <6 years at BMT } • Underlying diagnosis } eg thalassaemia, FA } → greater • Poor nutrition } growth • Pubertal delay / arrest } impairment • High total RT dose } • Prior cranial RT } • ?Unfractionated TBI (especially → hypothyroidism) • cGvHD (→ growth impairment; also → autoimmune disease → thyroid disease or diabetes) • Steroid treatment (→ growth impairment)	At Long Term Follow Up and Endocrine clinics	

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
Gonadal / Reproductive • Female • Male	• RT to field including gonads (and uterus) • Chemotherapy, especially alkylating agents (see list in *Gonadal – Female, Male*)	Female and Male Routine evaluation needed even in absence of overt symptoms 1) Assess pubertal (Tanner) stage, including testicular examination (?soft) and volume (using orchidometer), in context of age and linear growth 2) Measure sex hormones (testosterone or oestrogen), gonadotrophins (FSH, LH) and inhibin B (if available) from approximately 10 years of age (**NB** Measurement of gonadotrophins unhelpful in pre-pubertal children) 3) Semen analysis when appropriate 4) Discuss risk of impaired fertility, adverse pregnancy outcome, early menopause 5) Advise that contraception is still advisable in view of possibility (albeit uncommon) of fertility See also *Gonadal – Female, Male*	1) Refer to Endocrinologist for assessment of requirement for hormone replacement treatment in patients with Leydig cell or ovarian failure 2) **NB** In females on hormone replacement treatment, consider trial off treatment at appropriate intervals (eg 4 yearly) to evaluate possible ovarian recovery 3) Discuss referral to Reproductive Medicine specialist for consideration of assisted reproduction technology in appropriate situations See also *Gonadal – Female, Male*
Female • Ovarian failure – delayed / arrested puberty, amenorrhoea, impaired fertility, increased risk of adverse pregnancy outcome, early menopause	Female • Older age at BMT • High total RT dose to gonads and uterus • Unfractionated TBI • High dose of alkylating agents		
Male • Germ cell failure - impaired fertility • Leydig cell dysfunction - delayed / arrested puberty • Erectile dysfunction **NB** Germ cell much commoner than Leydig cell failure	Male • Younger age at BMT (Leydig cell dysfunction) • High total RT dose to gonads • High dose of alkylating agents	Female and Male At Long Term Follow Up and Endocrine clinics 1) Assessment of pubertal stage and growth at least every 3-6 months until completion of puberty and growth 2) Measurement of sex hormones and gonadotrophins annually **NB** Testicular volume is reduced in boys with germ cell failure, and is therefore not a reliable indicator of pubertal progression	
NB Ovarian recovery is well documented, but recovery of spermatogenesis rare with most classic BMT conditioning regimens. Some lower dose regimens may have higher gonadal recovery rates.			
Neurological (CNS, PNS, spinal) • Leucoencephalopathy • Vasculopathy – CVAs, vasculitis, 'migraine-like' episodes • CNS infections • Benign and malignant CNS tumours • Peripheral neuropathy (thalidomide – predominantly sensory → paraesthesia, numbness)	• RT to field involving brain (TBI, cranial, craniospinal) • Chemotherapy – methotrexate (systemic or intrathecal) • Immunosuppressive treatment – thalidomide (peripheral neuropathy)	Routine evaluation needed even in absence of overt symptoms 1) History and examination – especially headaches, raised intracranial pressure, cranial nerve and motor function, gait, peripheral nerve function 2) High index of suspicion, especially in higher risk patients See also *Neurological*	1) Further investigation and treatment as appropriate, depending on clinical event See also *Neurological*
	• High cumulative RT dose (leucoencephalopathy, tumours) • cGvHD (vasculitis) • Prolonged immunosuppression (CNS infection)	At Long Term Follow Up clinic See *Neurological*	

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
Neuropsychological • Functional impairment • Cognitive impairment	• RT to field involving brain (TBI, cranial, craniospinal) • Chemotherapy – methotrexate (systemic or intrathecal), busulphan	Evaluation needed in response to symptoms or school difficulties 1) History and examination – memory, attention, intelligence, visual-spatial, verbal and fine motor function, neurological deficit 2) High index of suspicion, especially in higher risk patients See also *Neuropyschological*	1) Liaise with school in all at risk patients 2) Refer for Neuropsychological or Educational Psychological assessment in high risk patients or those with suspicious symptoms or signs – where appropriate, aim for Statement of Educational Needs and / or extra time in examinations See also *Neuropyschological*
	• Young age (especially <3 years) at treatment • Female gender • High cumulative RT dose • Short interval between two RT treatment courses • Longer duration of follow-up	At Long Term Follow Up clinic **NB** Toxicity (especially cognitive impairment) may only become evident after prolonged follow-up	
Cardiovascular • Echocardiographic abnormalities • ECG abnormalities • Myocardial toxicity • Pericardial disease • Valvular disease	• Chemotherapy – mainly anthracyclines, but also high-dose cyclophosphamide, other alkylating agents • RT to field involving heart or mediastinum (including TBI)	Routine evaluation needed even in absence of overt symptoms See *Cardiac*	1) Advise against smoking See also *Cardiac*
	• Pre- / peri-BMT iron overload (eg thalassaemia, aplastic anaemia) • Sepsis	At Long Term Follow Up clinic See *Cardiac*	
Respiratory • Obstructive disease • Restrictive disease – ranging from isolated diffusion to classical restrictive defect • Late-onset pulmonary syndrome (with several underlying histologies, eg BO, BOOP, IP)	• Chemotherapy – especially bleomycin, busulphan, methotrexate, nitrosoureas • RT to field including lungs (including TBI, craniospinal, mediastinal, mantle)	Routine evaluation needed even in absence of overt symptoms 1) History and examination – exercise tolerance, smoking 2) Perform PFTs (see below) 3) Consider CXR if symptomatic or if PFTs severely abnormal 4) High index of suspicion for cGvHD, especially in higher risk patients – look carefully for other features **NB** Patients are often aymptomatic even in the presence of severe pulmonary disease	1) If symptomatic or if abnormal PFTs, a) refer to Respiratory specialist, b) consider high resolution CT scan 2) Consider immunosuppressive treatment in chronic pulmonary disease associated with cGvHD 3) Advise against smoking
	• cGvHD – associated with obstructive disease, may also exacerbate restrictive disease • Pulmonary infection – before, during or after BMT • Thoracic surgery may increase effects of pulmonary toxicity	1) Perform CXR as indicated above 2) Ideally perform baseline PFTs before BMT 3) Repeat PFTs 1 year post-BMT (earlier if symptomatic) 4) Repeat PFTs annually if abnormal or if new symptoms 5) Repeat PFTs may be performed less frequently (eg 3-5 yearly) if asymptomatic and initial post-BMT PFTs normal	

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
Gastrointestinal • Nausea, vomiting, diarrhoea, abdominal pain, weight loss • Oesophageal stricture ➔ dysphagia • Intestinal malabsorption • Pancreatic malabsorption	• Intestinal infection • cGvHD	Evaluation only needed in presence of overt symptoms 1) History and examination – bowel habit, nutritional status, weight 2) High index of suspicion for cGvHD, especially in high-risk patients – look carefully for other features 3) Faecal samples – microbiology (including ova, cysts, parasites), virology, biochemical investigation of malabsorption	1) Discuss with / refer to Gastroenterologist to consider imaging and / or endoscopy 2) Consider immunosuppressive treatment in chronic gastrointestinal disease associated with cGvHD See also *Gastrointestinal*
	• Previous GIT surgery • RT to field including GIT (including TBI)	At Long Term Follow Up clinic See *Gastrointestinal*	
Hepatic • Cholestasis, may progress to irreversible liver disease • Acute non-infectious hepatitis • Sequelae of viral hepatitis • Sequelae of hepatic VOD (long term outcome poorly documented in literature but chronic sequelae probably very rare)	• GvHD (acute or chronic) – usually presents with cholestasis, rarely with acute non-infectious hepatitis • Chemotherapy – alkylating agents (especially busulphan), actinomycin D, methotrexate, thiopurines (especially 6TG) (➔ VOD) • Previous viral hepatitis – usually B or C (both now uncommon in UK)	Routine evaluation needed even in absence of overt symptoms 1) History and clinical examination – jaundice, hepatosplenomegaly 2) Measure LFTs 3) High index of suspicion for cGvHD in patients with cholestasis or acute hepatitis – look carefully for other features See also *Hepatic, Recipients of blood products*	1) Viral detection / serology – hepatitis B, C, other viruses as appropriate 2) Autoantibodies to exclude other causes of acute non-infectious hepatitis 3) Assessment of iron status – ferritin, further investigation as clinically indicated 4) Discuss with / refer to Hepatologist re management of hepatic GvHD (requires immunosuppressive treatment) or other hepatic sequelae See also *Hepatic, Recipients of blood products*
	• Risk factors for hepatitis B or C, including blood transfusion prior to 1991 (hepatitis C) • Pre- / peri-BMT iron overload (eg thalassaemia, aplastic anaemia)	At Long Term Follow Up clinic See *Hepatic, Recipients of blood products*	

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
Renal • Radiation nephritis – chronic glomerular impairment, hypertension, anaemia, haematuria • Glomerular impairment • ?Glomerular hyperfiltration • Proximal tubular impairment • Isolated hypertension • Proteinuria, nephrotic syndrome • Cancer-associated haemolytic uraemic syndrome (C-HUS)	• RT to field including kidneys (including TBI, abdominal, flank) • Chemotherapy – especially platinum agents, ifosfamide, nitrosoureas, ?melphalan • Very intensive chemotherapy conditioning regimens (C-HUS) • Other nephrotoxins – anti-infectives, immunosuppresives	Routine evaluation needed even in absence of overt symptoms See *Renal* for detailed investigation schedule In particular, ensure: 1) Measure BP 2) Measure U+Es 3) Perform urinalysis for proteinuria and haematuria 4) If positive for proteinuria (≥++), measure urine protein : creatinine ratio (UP/UC) in spot urine sample 5) High index of suspicion for cGvHD in patients with proteinuria / nephrotic syndrome – look carefully for other features	1) Consider immunosuppressive treatment in nephrotic syndrome associated with cGvHD 2) Consider GFR measurement (accurate technique) if high creatinine; discuss with Nephrologist 3) Discuss with / refer to Nephrologist if haematuria 4) Discuss with / refer to Nephrologist if persistent proteinuria (UP/UC > 100 mg/mmol, or > 50 mg/mmol for ≥ 1 year) to consider treatment with ACE inhibitor ± angiotensin II blocking agent See also *Renal*
	• ARF during BMT • Hepatic VOD during BMT • Previous nephrectomy • ?Young age (ifosfamide) • cGvHD – associated with proteniuria / nephrotic syndrome	At Long Term Follow Up clinic See also *Renal*, but more specifically: 1) Measure BP at least annually 2) Measure U+Es annually	
Lower urinary tract • Haemorrhagic cystitis	• RT to field including lower urinary tract (including TBI, abdominal, pelvic, spinal) • Chemotherapy – cyclophosphamide, ifosfamide,	Routine evaluation needed even in absence of overt symptoms See *Lower Urinary Tract* In particular, ensure: 1) Perform urinalysis for haematuria	See *Lower Urinary Tract*
	• Viral infection – CMV, adenovirus, papovavirus • cGvHD - ?due to association with immunosuppression and viral infection • Previous lower urinary tract surgery	At Long Term Follow Up clinic See *Lower Urinary Tract*	

SYSTEM • OUTCOMES	CAUSES HIGHER RISK FACTORS	CLINICAL EVALUATION FREQUENCY OF FOLLOW UP	FURTHER ACTION
Musculoskeletal • Sclerodermatous joint contractures <u>Muscular</u> • Polymyositis • Weakness <u>Skeletal</u> • Avascular necrosis (AVN) • Osteochondroma (OC) • Reduced BMD • Slipped epiphysis • Scoliosis	<u>Muscular / musculoskeletal</u> • cGvHD <u>Skeletal</u> • RT to field including affected bone (AVN, OC) (including TBI) • Cranial RT (➔ GH deficiency) • Chemotherapy, especially methotrexate (reduced BMD) • Steroids (AVN, reduced BMD)	Routine evaluation needed even in absence of overt symptoms 1) History and examination – diet, exercise, fractures, joint movements and pain, muscle weakness, back pain, gait 2) High index of suspicion for cGvHD in patients with sclerodermatous joint contractures – look carefully for other features 3) Consider measurement of BMD by DEXA scan, especially in patients treated for GH deficiency or hypogonadism See also *Bone Density*	1) Review immunosuppressive treatment in musculoskeletal disease associated with cGvHD 2) Encourage calcium-rich diet and exercise, discuss with / refer to Specialist in Bone Disease in patients with reduced BMD 3) Perform MRI if suspicion of AVN 4) Discuss with / refer to Orthopaedic Surgeon in patients with AVN, OC, slipped epiphysis or scoliosis
	• Older age (AVN rare <10 years age) • Male gender (AVN) • Endocrinopathy (GH deficiency, hypogonadism both ➔ reduced BMD; GH deficiency also ➔ muscle weakness)	At Long Term Follow Up clinic 1) Ideally perform DEXA scan 1 year post-BMT, then at regular intervals especially in patients treated for GH deficiency or hypogonadism **NB** Need to interpret DEXA results using size-related reference ranges	
Skin • Wide range of features of cGvHD – erythema, hypo / hyperpigmentation, vitiligo, poikiloderma, lichenoid and / or sclerodermatous lesions • Alopecia • Benign pigmented naevi • Tumours – melanoma, squamous cell carcinoma (SCC)	• cGvHD • RT (skin in field) • Chemotherapy (all skin)	Routine evaluation needed even in absence of overt symptoms 1) History and examination – suspicious skin lesions 2) Photography of lesions where appropriate 3) High index of suspicion for cGvHD in patients with suspicious skin lesions – look carefully for other features See also *Skin*	1) Refer to Dermatologist for examination of suspicious skin lesions – consider biopsy / excision biopsy as appropriate 2) Review immunosuppressive treatment in skin disease associated with cGvHD 3) Encourage avoidance of excessive sunlight / UV light See also *Skin*
	• cGvHD – associated with skin SCC • Fanconi anaemia	At Long Term Follow Up clinic	

NOTES

a) Late adverse effects in patients who have undergone BMT may be due to treatment received before, during or after the BMT.
b) The shaded portion ("sub-row") of this column in each section (eg Quality of Life) refers specifically to Higher risk factors.
c) Cross references denoted in italics refer to the other sections of this Practice Statement.
d) The statement "At Long Term Follow Up clinic" assumes that this will enable regular evaluation at yearly (or occasionally two-yearly) intervals, unless there are specific indications for more frequent assessment (as discussed in the introductory comments to this Appendix, paragraph 5).
e) The shaded portion ("sub-row") of this column in each section (eg Quality of Life) refers specifically to Frequency of follow up.
f) Discussion with / referral to other specialists – although not explicitly stated, it is expected that paediatric specialists will be consulted unless patient age (adolescent or young adult) or local circumstances or expertise dictate otherwise.

ABBREVIATIONS

6TG	6-thioguanine
AML	acute myeloid leukaemia
ARF	acute renal failure
AVN	avascular necrosis
BMD	bone mineral density
BO	bronchiolitis obliterans
BOOP	bronchiolitis obliterans with organising pneumonia
cGvHD	chronic graft-versus-host disease
C-HUS	cancer-associated haemolytic uraemic syndrome
CMV	cytomegalovirus
CVA	cerebrovascular accident
CXR	chest X-ray
FA	Fanconi anaemia
FBC	full blood count
GIT	gastrointestinal tract
GH	growth hormone
HbA_{1c}	glycosylated haemoglobin
IP	interstitial pneumonia
LFTs	liver function tests
MDS	myelodysplasia
OC	osteochondroma
RT	radiotherapy
SCC	squamous cell carcinoma
T_4	thyroxine
TBI	total body irradiation
TFTs	thyroid function tests
TLI	total lymphoid irradiation
TSH	thyroid stimulating hormone
U+Es	urea, creatinine and electrolytes

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Chronic GvHD

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TABLE II
CHECK LIST FOR HISTORY, EXAMINATION, SURVEILLANCE INVESTIGATION

Consider the following regularly* at Long Term Follow Up clinic
Additional investigations may be appropriate if abnormal symptoms / signs

History
School / employment
Quality of life
Growth
Nutrition, weight gain
Pubertal development } at appropriate
Fertility issues } age / time
Joint pain (especially hip, knee)
Vision
Dental health
Compliance with medications eg anti-infective prophylaxis
Immunisation up to date (as appropriate)
Health education as appropriate, including smoking, sunlight, breast examination

Examination
Height (including sitting height if possible), } 3-6 monthly until
weight, calculate height velocity } puberty and
Pubertal assessment (Tanner stage) } growth completed
Skin (cGvHD, naevi, suspicious lesions) – consider clinical photography
Thyroid palpation
CNS examination
Ophthalmoscopy (cataracts)
Blood pressure

NB Wide variety of symptoms / signs of cGvHD

Investigations
FBC
Biochemical profile (incl U+Es, LFTs, albumin, protein, calcium, phosphate, magnesium)
Thyroid function tests (T_4, TSH)
LH, FSH, oestradiol† / testosterone } after 10 years
Inhibin B (if available) } age
Fasting glucose and lipids
HbA_{1c}
Immunoglobulins, lymphocyte subsets (only if clinical concern about delayed or poor immune reconstitution)
IGF-1 } in TBI recipients if concern
Bone age } about growth
Urinalysis (haematuria, proteinuria, glycosuria)
?Urine cytology
Echocardiogram (annually if abnormal, 3-5 yearly if normal)
Pulmonary function tests (annually if abnormal or if new symptoms, 3-5 yearly if normal and no symptoms)
Chest X-ray (if symptomatic or PFTs severely abnormal)
?Bone mineral density by DEXA (especially in patients treated for GH deficiency or hypogonadism)

* eg yearly (see introductory notes above) except where indicated otherwise – see Table I for further details
† not helpful if on hormone replacement treatment

Appendix C

FACTS OF PUBERTY

FEMALE

Background

- Oogonia arising from the primordial germ cells in the yolk sac reach a complement of 6-7 million by the sixth month of gestation; these represent the total fixed number of germ cells available. Primordial follicles consist of a primary oocyte surrounded by a single layer of spindle-shaped cells. By the time of birth, the pool of primordial follicles has already been reduced to 2-4 million by ongoing apoptosis and further attrition leaves approximately 400,000 by the time of menarche.

Puberty

- The onset of normal female puberty is characterised by the appearance of breast buds (breast stage 2, B2) at a mean age of 11.4 years, but ranging from as early as 8.4 years age to as late as 13.5 years. Any girl with breast buds before 8.4 years age has precocious puberty, whilst the absence of breast development in a girl older than 13.5 years requires endocrine assessment to ascertain the cause of the delay.
- During childhood, increased amplitude, frequency and duration of gonadotrophin pulsatility, will result in consonant pubertal progression, taking an average of two years to menarche (at B3 or B4), at mean age 12.4 (range 10-14.5) years.
- The attainment of breast stage 4 (B4) is a prerequisite for the onset of menstruation.
- For the first year after menarche, menstrual cycles are often anovulatory but ovulatory cycles, and thus the potential for fertility, can occasionally occur in girls whose sexual development is not quite complete.

Puberty and growth

- The timing of the onset of the growth spurt relative to the onset of puberty differs in a characteristic fashion between the sexes, occurring earlier in girls (breast stage 2 and 3) than in boys. The spinal component is an important part of the growth spurt.
- After the onset of menarche, only 3-5 cms of growth in height remain.
- Loss of harmony in pubertal development occurs if the relationship between height velocity and pubertal stage is lost, ie: a girl who is breast stage 2-3 should have a growth spurt (10-16 cm/yr).
- Bone age is a good guide to how much growth is past and how much is left to come. If bone age is advanced relative to chronological age, the height prediction is reduced. Bone age cannot predict the onset of puberty or the timing of the peak of the adolescent growth spurt.

MALE

Background

- The seminiferous epithelium of normal infant and child testes consists of immature Sertoli cells and spermatogonia. Primary spermatocytes, which degenerate and do not progress to spermatozoa, have been identified in some boys between the ages of 4-13 years.

Puberty

- Spermarche occurs at a median age of 13.4 (range 11.7-15.3) years at a time when median testicular size is 11.5 (range 4.7-19.6) ml.
- The prepubertal testis is approximately 2 ml in volume. The onset of puberty begins with enlargement of the testis (4 ml volume) at approximately 11.4 years. The longitudinal growth spurt starts when the testes are approximately 8 ml and is maximal at approximately 12 ml.
- The normal adult testis is 15 to 25 ml. Azoospermia is likely if the volume of each adult testis is 10 ml or less.

Puberty and growth

- The timing of the onset of the growth spurt relative to the onset of puberty differs in a characteristic fashion between the sexes, occurring earlier in girls than in boys (10-12 ml volume testes). The spinal component is an important part of the growth spurt.
- Loss of harmony in pubertal development occurs if the relationship between height velocity and pubertal stage is lost, ie: a boy with 8-10 ml volume testes should have a growth spurt (10-16 cm/yr).
- Bone age is a good guide to how much growth is past and how much is left to come. If bone age is advanced relative to chronological age, the height prediction is reduced. Bone age cannot predict the onset of puberty or the timing of the peak of the adolescent growth spurt.

REFERENCES

Guideline 1) http://www.sign.ac.uk/pdf/sign76.pdf ("Long term follow up of survivors of childhood cancer. A national clinical guideline")

Appendix D

FACTS OF FERTILITY

FEMALE

- Regular menses with appropriate basal gonadotrophin and sex steroid levels for stage of cycle are likely to be associated with ovulatory cycles.
- Irregular cycles with inappropriate gonadotrophin or sex steroid levels for stage of cycle may be associated with ovulatory cycles.
- In women exposed to gonadotoxic agents the window of fertility may be reduced by a premature menopause.

MALE

- A testicular volume of 10 mls or less in a normally virilised male is likely to be associated with a low sperm count.
- A persistently elevated FSH level is suggestive of infertility.
- A normal testicular volume in conjunction with a normal basal FSH level does not guarantee a normal sperm count.
- There is evidence of reversibility of low sperm counts with time in some patients.

REFERENCES

Guideline 1) http://www.sign.ac.uk/pdf/sign76.pdf ("Long term follow up of survivors of childhood cancer. A national clinical guideline")

Appendix E

IMMUNISATION AFTER COMPLETION OF TREATMENT

Immunisation six months and later after completion of standard chemotherapy

- **At 6 months following completion of treatment**, administer an **additional booster** of diphtheria, tetanus, **acellular** pertussis, inactivated polio vaccine (IPV), Haemophilus influenzae type b conjugate vaccine (Hib), Meningococcal C and MMR vaccines. Subsequent routine booster doses (eg pre-school) will not be necessary if they are scheduled to be given within one year of this additional dose.
- If patient has previously had BCG, and is considered to be in a high risk group for tuberculosis, check tuberculin test and if negative, revaccinate. If patient has not previously had BCG, immunise according to local policy. Ensure that primary health care team is informed.
- High risk groups for tuberculosis (TB) are:
  - Families with an ethnic minority background from a country with an incidence of tuberculosis of greater than 40 per 100,000 per year.
  - Patients travelling for over a month to a country with an incidence of tuberculosis of greater than 40 per 100,000 per year.
  - Household contact or prolonged close contact with an individual with tuberculosis.

Re-immunisation of allogeneic haemopoietic stem cell transplant recipients
General principles

- Re-immunisation should commence:
  - 12 months after a HLA-identical sibling donor allogeneic or a syngeneic haemopoietic stem cell transplant.
  - 18 months after any other allogeneic haemopoietic stem cell transplant.
- Providing that:
  - There is **no evidence** of active chronic GVHD, and
  - The child has been off **all** immunosuppressive treatment (eg steroids, cyclosporin A) for **at least 6** months (12 months before administering any live vaccines), and
  - The child has been off intravenous immunoglobulin (IVIg) for **at least 3** months.
- However, in patients with chronic GVHD not receiving IVIg, consider the use of non-live vaccines.

See next page for specific details and timing

HLA-identical sibling donor allogeneic or syngeneic haemopoietic stem cell transplant

- At 12 months post-haemopoietic stem cell transplant, administer:
  - Diphtheria, tetanus, acellular pertussis – 3 doses at monthly intervals.
  - IPV - 3 doses at monthly intervals.
  - Hib - 3 doses at monthly intervals.
  - Meningococcal C - 3 doses at monthly intervals.
- At 15 months post-haemopoietic stem cell transplant, administer:
  - Pneumococcal vaccine – give conjugate vaccine initially, followed by polysaccharide vaccine once the child is 24 months post-haemopoietic stem cell transplant.
    - If child under 24 months age, give 3 doses of conjugate vaccine at monthly intervals (NB polysaccharide vaccine to follow later – see below).
    - If child over 24 months age, give 2 doses conjugate vaccine at monthly intervals (NB polysaccharide vaccine to follow later – see below).
- At 18 and 24 months post-haemopoietic stem cell transplant, administer:
  - MMR (providing that at least 12 months off all immunosuppressive treatment) – these 2 doses should usually be given with a minimum 6 month interval, but the 2nd dose can be given 4 weeks after the 1st in the event of a measles outbreak.
- At 24 months post-haemopoietic stem cell transplant, administer:
  - Polysaccharide pneumococcal vaccine (see above) – 1 dose.
- Every autumn, administer:
  - Influenza vaccine (for as long as the patient remains clinically immunocompromised or is considered to be at increased risk from influenza virus infection).
- BCG immunisation should be avoided unless there is a clear case of need (eg travel to or residence in a country with an incidence of TB greater than 40 per 100,000 per year), and good evidence of immune function recovery (no history of serious infections, satisfactory serum immunoglobulin concentrations, CD4 lymphocyte numbers, lymphocyte function testing), with no evidence of chronic GvHD.

Any other allogeneic haemopoietic stem cell transplant

Re-immunisation schedule as above, but starting and continuing 6 months later (ie starting at 18 months post-transplant).

Re-immunisation of autologous haemopoietic stem cell transplant recipients

- Re-immunisation programme should commence 1 year after an autologous haemopoietic stem cell transplant.
- The schedule is identical to that for "HLA-identical sibling donor allogeneic or syngeneic haemopoietic stem cell transplant" (see above).

REFERENCES

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Appendix F

FOLLOW UP PROTOCOL LIST

- ☐ 1. Quality of life
- ☐ 2. Secondary malignancy
- ☐ 3. Recipients of blood products
- ☐ 4. Neurological
- ☐ 5. Neuropsychological
- ☐ 6. Visual
- ☐ 7. Auditory
- ☐ 8. Craniofacial / Dental
- ☐ 9. Hypothalamic-pituitary axis
- ☐ 10. Thyroid
- ☐ 11. Gonadal – female
- ☐ 12. Gonadal – male
- ☐ 13. Spine
- ☐ 14. Cardiac
- ☐ 15. Respiratory
- ☐ 16. Breast tissue
- ☐ 17. Gastrointestinal
- ☐ 18. Hepatic
- ☐ 19. Absent or dysfunctional spleen
- ☐ 20. Renal
- ☐ 21. Lower urinary tract
- ☐ 22. Bone density
- ☐ 23. Skin
- ☐ 24. Skin, bone, vascular, soft tissue in radiotherapy field
- ☐ 25. Major surgical procedure, including endoprosthesis

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Appendix G

TREATMENT SUMMARY

Current Name	Date of Birth
Name at Diagnosis	Hospital Number
Diagnosis	Site(s)
Date of Diagnosis	Protocol
Date of Recurrence	Site(s)
Relapse Protocol	Date of Treatment Completion

Chemotherapy (include dates completed, and dose of anthracyclines and alkylating agents)

Radiotherapy

Date	Site	Dose	Fractions
Date	Site	Dose	Fractions

Bone Marrow Transplant

Date	Allo / Auto	Allo Donor / HLA matching	
Chemotherapy Conditioning (include doses)			
TBI / Other Radiotherapy Conditioning	Site	Dose	Fractions
Acute GvHD (Grade, site)	Chronic GvHD (Grade, site)	Treatment	

Surgery Details
Complications during treatment
Complications after treatment completion
Parental height: Father Mother
Familial factors / Syndromes

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Appendix H

INVESTIGATIONS

Tests	Dates					
Psychological assessment						
Ophthalmological review						
Audiogram, ENT / Audiology review						
Craniofacial / dental review						
Assessment of hypothalamic pituitary axis						
Thyroid function tests						
Assessment of gonadal function						
Spinal review						
Echocardiogram						
Pulmonary function tests						
Breast imaging						
Liver function tests						
Renal function investigations						
Urinary tract investigations						
Assessment of bone density						
Skin examination / photography						
Surgical review						
Review immunisation status						

Appendix I

INDEX

ENDOCRINE CARE

Genotropin® (somatropin, rbe). Abbreviated Prescribing Information. Genotropin MiniQuick 0.2 mg. Genotropin MiniQuick 0.4 mg. Genotropin MiniQuick 0.6 mg. Genotropin MiniQuick 0.8 mg. Genotropin MiniQuick 1 mg. Genotropin MiniQuick 1.2 mg. Genotropin MiniQuick 1.4 mg. Genotropin MiniQuick 1.6 mg. Genotropin MiniQuick 1.8 mg. Genotropin MiniQuick 2 mg. Genotropin 5.3 mg. Genotropin 12 mg. Please refer to the SmPC before prescribing Genotropin**. Presentation: Genotropin MiniQuick:** Two compartment cartridge in single dose syringe containing powder and solvent for injection together with an injection needle. Each device contains either 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg or 2 mg somatropin (rbe). **Genotropin Cartridge:** Two-compartment cartridge for use in an injection device, Genotropin pen, or in a reconstitution device. The cartridges contain either 12 mg or 5.3 mg somatropin (rbe). Each cartridge also contains 0.3% m-cresol as preservative. Instruction on reconstitution plus use of devices is supplied separately as are the Pen, Genotropin ZipTip and Genotropin Mixer devices and any necessary consumables. **Indications:** Children: Treatment of growth disturbance due to insufficient secretion of growth hormone (GH) or associated with gonadal dysgenesis (Turner Syndrome) or chronic renal insufficiency (CRI) or in short children born Small for Gestational Age (SGA) with a birth weight and/or length below −2SD, who failed to show catch-up growth by 4 years of age or later. Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing. Adults: Replacement therapy in adults with pronounced GH deficiency defined as known pituitary pathology and at least one known deficiency of pituitary hormone not being prolactin. **Dosage and Administration:** Dose should be personalised for each individual. The subcutaneous injection site should be varied to prevent lipoatrophy. **Insufficient Secretion of GH in children:** 0.025–0.035 mg/kg/day. Higher doses have been used. **Prader-Willi Syndrome:** 0.035 mg/kg body weight per day. Daily doses of 2.7 mg should not be exceeded. **Gonadal Dysgenesis (Turner Syndrome):** 0.045–0.050 mg/kg/day. **CRI:** Approximately 0.045–0.050 mg/kg/day. Higher doses can be needed if growth velocity is too low. Dose correction can be needed after 6 months treatment. **Short children born SGA:** 0.035 mg/kg body weight per day until final height is reached. **GH Deficient Adults:** Start with low dose, 0.15–0.3 mg/day. The dose should be gradually increased as determined by the IGF-1 concentration. Clinical response and side effects may guide dose titration. Women (especially those on oral oestrogen) may require higher doses than men. **Contra-indications, Warnings etc:** Genotropin should not be used when any evidence of tumour activity exists and anti-tumour treatment must be complete. Genotropin should not be used for growth promotion in children with closed epiphyses. Genotropin should not be used in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment. Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with Genotropin. **Precautions:** Diagnosis and therapy should be initiated and monitored by suitably qualified and experienced doctors. Somatropin may induce insulin resistance and in some patients hyperglycaemia. Patients should be observed for evidence of glucose intolerance. As thyroid function may be affected, it is advisable to test this after starting treatment with somatropin and after dose adjustments. Signs of any relapse of malignant disease should be monitored. In patients with endocrine disorders, slipped epiphyses of the hip may occur. In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a funduscopy for papilloedema is recommended as some rare cases of benign intracranial hypertension have been reported and if appropriate treatment discontinued. In CRI, renal function should be below 50% of normal and growth followed for a year preceding therapy. Conservative treatment for renal insufficiency should have been established and be maintained during therapy. Discontinue GH after renal transplantation. There have been reports of fatalities associated with the use of growth hormone in paediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity (those patients exceeding a weight/height of 200%), history of respiratory impairment or sleep apnoea, or unidentified respiratory infection. Male patients with one or more of these factors may be at increased risk. Before initiation of treatment with somatropin in patients with Prader-Willi syndrome, signs for upper airway obstruction, sleep apnoea, or respiratory infections should be assessed. Patients should be monitored for signs of respiratory infections, which should be diagnosed as early as possible and treated aggressively. All patients with Prader-Willi syndrome should also have effective weight control before and during growth hormone treatment. Scoliosis is common in PWS and signs for scoliosis should be monitored. Experience of prolonged therapy in adults, patients with PWS and use in patients over 60 years is limited. In short children born SGA other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment. Not recommended to initiate treatment in SGA patients near onset of puberty. In acute, critically ill adult patients, GH may increase mortality. **Interactions:** In diabetes mellitus, insulin dosage may need adjustment. Somatropin has been reported to reduce serum cortisol levels, possibly by affecting carrier proteins or by increased hepatic clearance. The clinical relevance of these findings may be limited. Corticosteriod replacement therapy should be optimised before initiation of Genotropin therapy. **Pregnancy and Lactation:** There is no clinical experience of use during pregnancy. Interrupt treatment if pregnancy occurs. It is not known whether peptide hormones pass into breast milk, but absorption of intact protein from the infant GI tract is unlikely. **Overdosage:** None known. **Side Effects:** In adult patients, common adverse effects related to fluid retention; such as peripheral oedema, arthralgia and myalgia. These effects are mild to moderate, arise within the first months of treatment and subside spontaneously or with dose reduction. Transient local skin reactions in children are common. Carpal tunnel syndrome is uncommon (< 1/100 & ≥ 1/1000) in adults. Formation of antibodies of low binding capacity in approximately 1% of patients; in vitro chromosome aberrations of unknown clinical significance. Very rare cases (< 1/10,000) of leukaemia have been reported in GH deficient children treated with somatropin, but the incidence appears to be similar to that in children without GH deficiency. **Pharmaceutical Precautions:** Genotropin MiniQuick may be stored at or below 25°C by the end user for a single period of not more than 6 months. After reconstitution, use immediately or within 24 hours if stored at 2 – 8°C. Use Genotropin 12 mg within 3 weeks after reconstitution, 5.3 mg within 4 weeks after reconstitution. Store at 2–8°C. Protect from light. Do not freeze. **Legal Category:** CD (Sch 4, Part I), POM. **Pack / Basic NHS Price/PL No:** Genotropin MiniQuick 0.2 mg x 7 £32.46 0022/0186. Genotropin MiniQuick 0.4 mg x 7 £64.91 0022/0187. Genotropin MiniQuick 0.6 mg x 7 £97.37 0022/0188. Genotropin MiniQuick 0.8 mg x 7 £129.82 0022/0189. Genotropin MiniQuick 1 mg x 7 £162.28 0022/0190. Genotropin MiniQuick 1.2 mg x 7 £194.74 0022/0191. Genotropin MiniQuick 1.4 mg x 7 £227.19 0022/0192. Genotropin MiniQuick 1.6 mg x 7 £259.65 0022/0193. Genotropin MiniQuick 1.8 mg x 7 £292.11 0022/0194. Genotropin MiniQuick 2 mg x 7 £324.56 0022/0195. Genotropin 5.3 mg x 1 £122.87 0022/0085. Genotropin 12 mg x 1 £278.20 0022/0098. **PL Holder:** Pharmacia Laboratories Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK. **Further information is available on request from:** Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. **Date of preparation:** Dec 2004. **Company reference:** GN3_0.

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Prescribing information can be found on the inside back cover

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