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■ 特集 小児がん治療の晩期障害と対策

小児がん治療後のよりよい生活—Erice 宣言の重要性

石 田 也寸志*

はじめに

小児期に発症するがんの治療成績の進歩は顕著で，最近の5年寛解生存率は70～80%に及び[1]，わが国にも数万人以上の小児がんの長期生存者（以下，小児がん経験者）が存在し，成人期を迎えた小児がん克服者の数は若年成人の400～1,000人に1人にあたるといわれている[2]。しかしこれまでの報告では，診断後5年が経過した後でも小児がん経験者の死亡率は統計学的に有意に高く，標準化死亡比は4～17であり，5年以上生存した小児がん経験者の多く（60～70%）は，種々の晩期合併症を抱えていると言われている[3]。

2006年10月27日～29日の3日間，イタリアのSicily島Ericeにおいて，International Berlin-Frankfurt-Munster（I-BFM）のEarly and Late Toxicity Educational Committee（ELTEC）主催によるワークショップが開催された[4]。参加者はヨーロッパ13カ国から招待された45名（小児がん専門医，心理学者，看護師，疫学者，そして小児がん経験者とその親）に加え，北米からの小児がん専門家5名である。このワークショップの目的は，**表1**に示したように小児がんにおいて“治癒”という言葉はふさわしいか，もしそうならそれはいつなのか，また継続的なフォローアップとケアの必要性が考えられる時期とその根拠について，小児がん経験者や社会とどのように対話していくべきか，今後どのような研究がどのくらい必要かが話し合われた。

小児がんの治癒およびそのケアには長時間を要するが，目標は小児がん経験者が病気から立ち直り，十分に機能を回復し，望ましいQOLのもと自立した一人の成人として，同年代の人々と同じように社会に受け入れられるようになることである。Ericeにおける3日間の会議の結果，**表2**に示したような10項目の宣言が発表された。本稿では，主催者HauptのErice宣言を広く世界中に流布させたいという意向を受けて，この宣言の内容を概説し，小児がん治療後のよりよい生活について考察する。

表1 Ericeワークショップの目的

1．Is the term “cure” appropriate?
　-if yes, when and to what dose it apply?
2．How to care
3．How to communicate
　-To “survivors”
　-To the Society
4．How and how much research is needed

Ⅰ．声明文の説明

Hauptの論文[4]に従って，それぞれ1項目ずつ説明を加える。

1）“治癒”というのは，原疾患である小児がんが治ることを意味するもので（**表3**），残存する障害や治療による副作用もしくはそれらの可能性があるかないかは問わない。これら治療の合併症は，原疾患とは別枠で考えられ，個々の患者特有の因子と治療関連のリスクベースケアによって，長時間をかけて対応されるべきものである。“治癒”は小児がん経験者と彼らを取り巻く社会で使用される言葉であり，これに対し“long-term survivor（長期生存者）”は注意を必要とする後遺症の存在を専門家に注意喚起する科学的研究や関連文献で使用されるべき言葉として今後も使用を続ける。

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表 2 Erice 宣言の概要

1. Cure refers to cure from the original cancer regardless of any potential for, or presence of, disabilities or side effects of treatment.
2. The communication of "cure" should occur in the context of a shared decision taking the individual circumstances into consideration.
3. Survivors and families have the right to be fully informed in person and in writing about being cured, as about the remaining risks of late effects. It is the responsibility of the pediatric cancer unit (PCU) to provide a summary of the characteristics of the disease, of treatments received, and of complications that may have occurred during therapy. The summary must be combined with suggestions on the type and timing of the follow-up evaluations.
4. Every PCU should have a well-structured "follow-up clinic" and a multidisciplinary team. When the survivor enters adulthood, he/she should be referred to an appropriate health care provider.
5. Evidence-based counseling requires the collection of research data on which to base recommendations.
6. Efforts should be made to strength coping skills of survivors and future concerns.
7. Some survivors are at an increased risk of developing conditions that need medical, psychological or social care. The health care system must address all these groups.
8. Parents and advocacy groups should be included as active members in the multidisciplinary health care team.
9. The general public needs to be made aware of and accept the reality of the cure of childhood cancer. The society should insure that survivors have equal access to education, jobs, insurance, and medical care.
10. Inequalities of current treatment strategies and cure rates, both within and between nations, remain a challenge for the international community to address.

(Haupt ら, 2007)[4]

表 3 "治癒" の概念

- It is not possible to provide an exact definition of cure that applies to all cancers.
- Cure refers to the original disease regardless of any potential for, or presence of, disabilities or side effects.
- Children treated for cancer can be considered cured when they give reached a time point at which the chance that they will die from their original disease is no greater than that of age peers in the general population of dying from any cause.
- The time to cure depends on tumor type, stage, and other biological factors. For some other tumors, attempting precision is unreliable because of underlying strong genetic factors involved in the causation of and response to the specific cancer.

<疫学的な視点からの定義>

When is a survivor considered cured from the original cancer?

-Evaluate conditional risks on surviving each year since diagnosis.

-Make decision when the risk becomes "almost zero" (evaluate the change in risk, and see when becomes negligible).

(Haupt ら, 2007)[4]

2) 小児がん経験者のケアには，診断，治療そして予後に関して十分な包み隠さない情報を保護者と本人へ提供することも含まれる。小児期あるいは思春期の小児がん経験者とその家族への "治癒" の告知は，担当する小児がん専門医によって，すべての関係者の同意と了解を得た後に，その小児がん経験者の個人的な背景を考慮したうえで行われる。

3) 小児がん経験者とその家族への種々のリスクに関する説明は，容易に理解できる言葉を用い，可能な限り前向きになれるよう表現に留意する。効果的な説明を行うためには，高度の人間関係に関する力量が必要になる。"治癒" また晩期合併症，原発がんの再発，あるいは二次がんの可能性に関

する説明は,本人と家族へ口頭で行うだけでなく,書面にても行う。原発がんへの治療が完了したら,小児がんチームの責任下で,疾患自体と治療中に発生した合併症（発症した場合）のまとめを本人とその親へ提供する。このまとめには原疾患および原疾患や治療に起因して起きる可能性のある晩期合併症と原発がんのフォローアップ検査の種類と時期に関しても提示されていなければならない。本人が成人した際には,生涯にわたってケアができる医療従事者へ紹介する。また小児がん治療に起因すると思われる問題が発症した場合は,最適な専門家へ紹介する。小児がんチームは可能な限りその患者のすべての医療記録をその専門家に提供しなければならない。また患者の長期にわたる記録を入手し,保管しておくことも小児がんチームの責務とする。

4）原疾患あるいは治療に起因する晩期合併症の監視も継続的なフォローアップシステムに組み込まれていなければならない。それには小児がんチームに配慮の行き届いたフォローアップ外来システムが構築され,多分野からの専門家（小児がん専門医師,看護師,心理学者,ソーシャルワーカー,必要と思われる関連分野の専門家）が関与するチームが編成されていなければならない。

5）小児がん経験者への的確で明確なアドバイスと支援の提供には,検査や研究によってさらなる情報収集の努力を行うことが小児がんチームに求められる。また研究の優先順位の決定には,小児がん経験者およびその家族と医療従事者との対話も必須となる。根拠に基づいたカウンセリングの実現には,アドバイスの根拠となる研究データの収集を必要とし,それらの研究結果はデータ提供者と小児がん経験者およびその家族へ提示されなければならない。それによって将来再び協力を得ることも可能となる。

6）治療中そして治療終了後も,小児がん経験者とその家族への組織的な支援をする努力が必要である。本人の年齢（理解度）に合わせて情報提供を行い,現在および将来に発生の可能性がある諸問題に対処する方策を提供することで励ましていくような努力である。ほとんどの小児がん経験者,およびその家族は直面する問題にはうまく対処している。だからこそ,さらにそのような力を補強することは,彼らが問題を直視し,それを乗り越え,立ち直る支えとなるであろう。そして将来に向かって,より力強く,自信を持って進むことができるであろう。とくに移行（transition）の際にはこのような支援が重要となる。移行とは医療形態の変化であり,主要な時期は,治療終了時,治療が終了し長期フォローアップケアプログラムに入ったとき,そして小児科から成人の医療システムに移るときである。この移行をスムーズに行えるように専門の相談者が配置されていなければならない。

7）前述したように,小児がん経験者の大半は直面した諸問題に比較的うまく対処しており,驚くべき立ち直りを示す比率も実際に高い。しかしながらその一方で,一般集団に比較すると医療的,心理的,あるいは社会的なケアを必要とするリスクが高まっている小児がん経験者も現存する。そのため医療ケアシステムは,どのような状況にあろうともすべての小児がん経験者に開かれたものでなければならない。

8）将来の計画や心理社会的介入の計画と実行に関する話し合いには,親や同胞,そして本人と親しい人々を常に積極的に取り込むことが重要である。そのうえで,小児がん経験者やその家族は,他の小児がん経験者やその家族と情報を共有し,方策をともに考え,小児がん経験者を勇気づける存在としても大きな役割を担うことができ,望ましい医療サービスの計画と実行にも協力者となりうる。そのため親や支援グループを集学的医療ケアチームのメンバーとして加えるべきである。

9）社会全体が,小児がんは治癒する時代となったことを知り,その現実を認めなければならない。過去30年間に小児がん治療は目覚しい進歩を遂げ,数多くの小児がん経験者を世に送り返した。その小児がん経験者達は,学業を修了し,大人の世界へと足を踏み入れ,社会に不可欠な存在として前向きに生活しており,そのような小児がん経験者の数は年々増加している。それゆえ小児がん経験者も教育,職業,保険そして医療ケアを一般集団と同様に受けることができる社会とならなければならない。

10) 同じ国のなかでも，そして国の違いによっても，治療法と生存率に格差が出ているのが現状で，それは社会経済的な背景と医療資源の配分の違いが大きくかかわっており，このことは国際的な課題として今後も世の中に喚起していく必要がある。

II. 考　察

すべての小児がんの治癒を一律に正確に定義することは不可能であるが，小児がん克服者の数が増加している現状から，“治癒”という言葉を以下のように定義することで Erice 会議参加者間の同意が得られた。小児がんの治癒とは，「身体的障害や治療の副作用の有無やその可能性のあるなしにかかわらず，原疾患の状況のみに帰する。そして小児がん治療を受けた子どもの原疾患が原因で死につながる確率が，一般集団での同年齢児の死亡（原因のいかんにかかわらず）確率よりも高いとは認められなくなった時点で，その子どもは小児がんが治癒したと考えられる」というもの（表3）である[4]。

さまざまな小児がんがあり，がんの種類によって異なるものの，ある一定の年数が経過すれば，その小児がん経験者は治癒とみなされる。“治癒”とされる時期は，がんの種類，病期，そしてその他の生物学的要因によって決定される。一般には診断後，再発なしで 2〜10 年経過すれば治癒とみなされる。またがん発症の原因として，強い遺伝的素因が関与している場合には“治癒“の正確な定義づけは難しいと思われる。

2007 年 11 月のブダペストの ELTEC 会議の席上で，Byrne により Piedmont 小児がん登録のデータから上記の作業仮説に基づき小児がんの治癒の時期を推定する試みが発表された[5]。まだ症例数も少なく，あくまでプレリミナリーではあるが，**表 4** に示したように原疾患による違い以外に，治療年代による違い（最近の治療になるほど晩期の再発が減少する），発病年齢による違いなどもある。2008 年の I-BFM の年次総会でも引き続きイギリスのデータを元にして検討が行われる予定であり，今後小児がん経験者や家族に再発の危険性を説明する際の重要なエビデンスになることが期待される。一方，治癒と判定されるまでの年数がかなり長い疾患などでは，このようなデータが公開されることで，かえって保険加入の際の障害となる危険性もあり，今後慎重に対応していく必要がある。

表 4　疫学データから“治癒”と判断されるために必要な年数*

	カテゴリー	急性リンパ性白血病	脳腫瘍
治療年代	1967〜1978	10 年**	13 年
	1979〜1988	8 年	10 年
	1989〜1999	5 年	7 年
診断時年齢	<1 歳	2 年	2 年
	1〜4 歳	8 年	8 年
	5〜9 歳	9 年	10 年
	10〜14 歳	7 年	13 年
性別	男性	9 年	11 年
	女性	9 年	9 年

*プレリミナリーな解析であり，あくまで 1 つの例であることに注意（Byrne）[5]。
**表の見方としては，1967〜1978 年に治療した急性リンパ性白血病の症例は，10 年で原疾患が原因で死につながる確率が，一般集団での同年齢児の死亡確率と同一になる，というふうに解釈する。

また最近報告された Oeffinger ら[6]による北米の Childhood Cancer Survivor Study と Geenen ら[7]のオランダの報告によると，少なくとも 1990 年代までに治療を受けた小児がん経験者では約 3 分の 2 以上の症例になんらかの晩期合併症を認めることが予想され，小児がん経験者では生涯に及ぶ長期フォローアップの重要性が再確認された[8]。長期フォローアップの推奨ガイドラインもいくつか報告されており[9,10]，多くは科学的なエビデンスに基づくものではあるが，医療経済的にコストベネフィットに叶うものであるかどうかはこれから検証していく必要がある[11,12]。

おわりに

2007 年に発表された Erice 宣言に基づき，小児がん治療終了後の長期ケアと治癒について考察を加えた。この宣言によると，診断や治療のまとめを提供し，必要時に適切な専門家に紹介するのは治療を担当した小児がんチームの責務であり，十分な情報交換の元に成人期のフォローに移行していけるようなシステム作りが望まれる。まだわが

国では小児がん治療後の長期フォローアップ体制作りは始まったばかりであるが，Erice 宣言にその目標が明確に示されていると考えられる。

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Achievement of a Better Life after Childhood Cancer Treatment ：The Importance of the Erice Statement

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I introduce the Erice statement, which deals with the cure and care of children with cancer after their treatment. The ten points reflect what my research group considers essential to achieve a better life for long-term survivors. According to the statement, it is the responsibility of the pediatric cancer unit to provide the treatment summary and refer the patient to the appropriate specialists if needed. We must communicate with childhood cancer survivors as well as their guardians to facilitate their smooth transition. "Cure" refers only to the original disease；risk-based long-term follow-up care should be provided for all survivors.

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Letter to the Editor

'Evaluation of swallowing function in Duchenne muscular dystrophy'

SIR – Although the prognosis of patients with Duchenne muscular dystrophy (DMD) has been poor for several decades, the recent introduction of non-invasive intermittent positive pressure ventilation (NIPPV) to treat respiratory failure in patients has resulted in an extension of life expectancy. Therefore, heart failure and feeding impairments have become more critical for these long-term survivors. Although the mechanisms underlying the respiratory and cardiac complications have been elucidated, the pathogenesis of the feeding impairments in DMD has not been clarified. So, this study aimed to evaluate the feeding abilities of patients with advanced-stage DMD using videofluorography (VF), which has been established as a standard method to evaluate swallowing function, and compare the results with their clinical symptoms.

Five patients with advanced-stage DMD were evaluated for this study. Patient age ranged from 18 to 24 years at examination, and all patients were non-ambulatory. Three patients needed NIPPV during sleep periods only, due to chronic hypoventilation, and one suffered from mild heart failure and had taken an angiotensin-converting enzyme inhibitor every day. Informed consent was obtained from all patients and their parents. A questionnaire for patients was prepared to evaluate any subjective symptoms of dysphagia. Feeding dysfunction was evaluated in four different phases: oral preparatory, oral, pharyngeal, and oesophageal.

The oral preparatory phase assessment targeted the difficulties in bringing food to the mouth or opening the mouth. In the oral phase, dryness of the mouth, impaired chewing, biting of the tongue, or difficulties in keeping food in the mouth were assessed. In the pharyngeal phase, we analyzed the repeated attempts to swallow, foods sticking in the throat, clearing of the throat, choking, or nasal reflux. Finally, in the oesophageal phase, regurgitation and heartburn were evaluated.

The severity of feeding dysfunction was graded as follows: –, never or rare; +, occasional (once per wk or less); ++, frequent (daily or many times per wk). The head and neck positions and overall postures were also evaluated in two phases: in the oral preparatory phase, we assessed the difficulty in bringing food to the mouth and opening the mouth; and in the oral phase, the inability to tighten the lips and the lower jaw movement during mastication were investigated. VF was performed in all five patients at our hospital as follows: the same food and liquids that patients had used daily were used, and mixed with the same amount of a non-ionic water-soluble contrast medium. In this examination, Iohexol (Daiichi Pharmaceutical Co., Tokyo, Japan) was used to minimize the risk of complications due to aspiration. Each patient was examined during the intake of liquids, and solid or soft foods respectively, based on the food texture they usually preferred. Quantitative evaluation of the swallowing movements at the oral and pharyngeal phase was performed using lateral fluoroscopic images. Observations were made according to previously described diagnostic characteristics.[1] The total examination time was less than 5 minutes.

Table I shows patients' feeding dysfunctions. In the oral preparatory phase, occasional difficulties in bringing food to the mouth were observed in all patients. In the oral phase, three patients occasionally bit their tongues due to an enlarged tongue. Only one patient reported impaired chewing although all patients preferred soft textured foods. In the pharyngeal phase, three patients frequently complained of difficulties in swallowing, food sticking in their throats, and/or needing to clear their throats. One patient experienced nasal reflux, and another choking. In the oesophageal phase, there was no complaint, including

Table I: Feeding dysfunction of the five patients with Duchenne muscular dystrophy

Patient number	*1*	*2*	*3*	*4*	*5*
Oral preparatory phase					
Difficulties in bringing food to the mouth	+	+	+	+	+
Difficulty in opening the mouth	–	–	–	–	–
Oral phase					
Dry mouth	–	–	–	–	–
Impaired chewing	++	–	–	–	–
Tongue biting	+	–	+	–	+
Pharyngeal phase					
Repeated attempts to swallow	+	++	++	–	–
Food sticking in the throat	–	++	++	–	+
Clearing the throat	–	+	+	+	–
Choking	–	–	+	–	–
Nasal reflux	–	–	–	–	+
Oesophageal phase					
Regurgitation	–	–	–	–	–

Severity of feeding dysfunction was graded as follows: –, never or rare; +, occasional (once per wk or less); ++, frequent (daily or many times per wk).

regurgitation or heartburn. In the evaluation of swallowing, two patients were in their wheelchairs, and three others used Japanese legless chairs. During the entire mealtime, all patients leant forward supporting their trunks using the adjustable table. While masticating, they swung their heads back and forth repetitively to aid bolus transport, and no patient was sitting upright and still. Three patients required some assistance during eating. Two others were able to bring food to their mouths on their own; however, the table was lined up with their mouths. Overall, all patients had difficulties bringing food to their mouths. They were able to close their lips tightly and move the lower jaw without any observable difficulty during mastication. The findings of the VF study are summarized in Table II. Malocclusion was seen in all patients. The mastication time ranged from 8 to 21 seconds. Food leaked into the pharynx during chewing, due to disturbed function of the tongue in all patients. They also exhibited weak pharyngeal contraction or vermicular movements to transport food. The mean pharyngeal transit times of the bolus were 0.15 to 0.42 seconds for liquids, 0.33 to 0.38 seconds for soft food, and 0.30 to 0.49 seconds for solid food. Elevations of the hyoid bone and the larynx on swallowing were observed in all patients, but the epiglottis did not tip downward to close the laryngeal vestibule in three patients due to insufficient elevation (less than the height of the C5 vertebra) of the hyoid bone. Moderate food retention was seen at the valleculae and piriform sinuses in four patients. Aspiration and penetration were not observed in any patient.

Feeding problems are major concerns in most patients with neuromuscular diseases, including DMD, during the course of the disease.[2] VF has been established as a standard method to evaluate swallowing function, but there are few studies reporting on the use of VF in DMD patients. Our study showed some discrepancies between the clinical symptoms and the results of the VF study, particularly in the oral preparatory and oral phases of patients with advanced DMD. Particularly, the VF study showed that all patients had apparent functional impairment, despite the limited number of complaints from these patients.

In a previous case–control study, a significant number of patients with DMD complained of upper gastrointestinal dysfunction compared to their age-matched controls.[3] These symptoms were noted in both the oral and pharyngeal phases. Among them, chewing difficulty was common and gradually progressed with age.[4] In our study, no patient reported any difficulty in opening their mouths, or keeping food in their mouths. Only one patient complained of chewing impairment. However, all patients exhibited malocclusion, struggled to manipulate food in their mouths, and showed insufficient movement of the tongue. These discrepancies might be due to patients' adaptation of their difficulties in feeding. More likely, patients gradually adjusted their diet to compensate for their feeding difficulties, and thus did not recognize the problems. The VF study showed that there were some food residues in the valleculae or piriform sinus in four patients, indicating a reduction in the strength of pharyngeal peristalsis, and it was noted that some food got 'stuck' in the throats of three patients. During swallowing, the epiglottis could not cover the larynx completely in three patients, and two patients showed incomplete elevation of the hyoid bone.[5] Only one patient experienced choking during daily meals, but the VF study did not indicate delayed food movement as the cause of choking. Penetration or aspiration was not seen in any patient. Therefore, it was suggested that apparent aspiration was not always present, although silent aspiration could not be excluded.

Patients with advanced DMD experience swallowing disturbance of various degrees, and they spontaneously prefer

Table II: Videofluorography of the five patients with Duchenne muscular dystrophy

Patient number	*1*	*2*	*3*	*4*	*5*
Oral phase					
Malocclusion	Yes	Yes	Yes	Yes	Yes
Mastication time for food, s	10	21	8	17	9
Incomplete closure of the tongue to the soft palate during mastication	Yes	Yes	Yes	Yes	Yes
Abnormal leakage of food to the pharynx during mastication	Yes	Yes	Yes	Yes	Yes
Weakness of pharyngeal contraction or vermicular movements	Yes	Yes	Yes	Yes	Yes
Pharyngeal phase					
Mean pharyngeal transit time of food (SD)					
Liquid, s	0.42 (0.16)	0.27 (0.17)	0.38 (0.13)	0.32 (0.16)	0.15 (0.10)
Soft food, s	0.38 (0.16)	0.33 (0.17)	NT	NT	NT
Solid food, s	NT	NT	0.30 (0.17)	0.49 (0.13)	0.47 (0.14)
Degree of hyoid bone elevation during swallowing (/height of the C5)	0.7	0.8	1.0	1.4	1.3
Incomplete closure of the epiglottis during swallowing	Yes	Yes	No	Yes	No
Retention of food in the valleculae or piriform sinuses	No	Yes	Yes	Yes	Yes
Penetration or aspiration	No	No	No	No	No

NT, not tested.

modified food textures. In the present study, they did not complain frequently about feeding, but the results of the VF examinations were worse than expected. Swallowing problems might be slowly progressive in patients with advanced DMD, therefore such patients might develop a risk of aspiration or asphyxia.

In conclusion, feeding impairments of various grades were observed in all patients, therefore, appropriate evaluations using clinical findings and VF examination, and early preventative management are needed for the safe oral feeding of patients with advanced-stage DMD.

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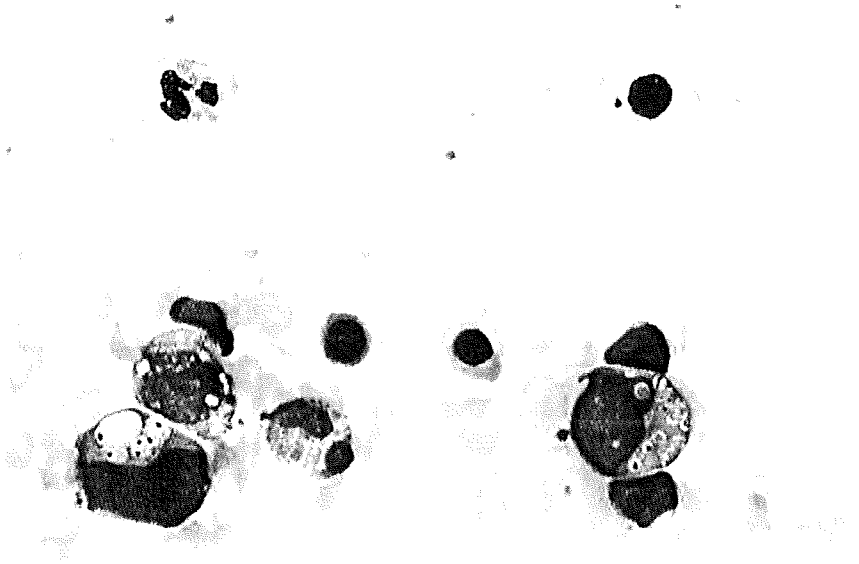

Chediak-Higashi 症候群

患児は，2歳2ヶ月の男児。易感染性と頭髪・皮膚の部分的白子症を主訴に来院した。祖母同士がいとこ婚。末梢血の May-Giemsa 染色で，好中球に二次顆粒分布異常，リンパ球には巨大なアズール顆粒を認めた。Peroxidase 染色で，好中球顆粒は強陽性・粗大顆粒状に染まり，リンパ球顆粒は陰性であった。α-naphtyl-butyrate-esterase 染色では，リンパ球の一部で強陽性に染色される細胞を認めた。PAS 染色はともに陰性であった。骨髄検査では，顆粒球系に著明な空胞形成と封入体様の異常顆粒を認めた。NK 活性は極めて低値であった。以上の所見から，Chediak-Higashi 症候群と診断した。

Chediak-Higashi 症候群は，1952 年に Chediak が新たな形態異常を伴う白血球異常症として報告した[1]。他方翌 1953 年，東音高秋田大名誉教授が東北大時代に巨大 peroxidase 顆粒を伴う先天異常疾患として同様の症例を報告した[2]。佐藤彰東北大名誉教授は，これらが同一疾患であるとして，1955 年に Chediak-Higashi 症候群と命名した[3]。また，1948 年に Steinbrinck によって報告された症例[4]も同一疾患と思われ，Chediak-Steinbrinck-Higashi 異常と呼ぶこともある。

Chediak-Higashi 症候群の原因は，細胞内顆粒輸送にかかわる Lyst 遺伝子の異常であることが明らかにされている。その結果，NK 細胞や細胞傷害性 T 細胞の細胞傷害活性の低下やメラニン色素異常による白子症が生じる。

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Original

Factors Affecting Final Height and Growth Hormone Provocation Tests in Survivors of Childhood Acute Lymphoblastic Leukemia who Underwent Cranial Irradiation

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頭蓋照射を受けた急性リンパ性白血病経験者における最終身長に影響を及ぼす因子と成長ホルモン分泌刺激試験の検討

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要　旨　頭蓋照射を受けた小児急性リンパ性白血病（ALL）経験者51名を対象に，最終身長に及ぼした因子，および成長ホルモン（GH）分泌刺激試験の結果について検討した．両親の身長から計算した目標身長と実際の最終身長との比（RFT）を求めた．RFTは，遺伝的な背景を加味した獲得最終身長の割合を表しているものと考え，この値を最終身長の評価に用いて検討を行った．RFTが0.95未満の経験者は13.7%，0.975未満は27.5%であった．RFTは診断時年齢と総副腎皮質ホルモン投与量と関係があったが，性別と頭蓋照射量とは関係を認めなかった．RFTが0.975未満の12名中の11名はGH分泌刺激試験の反応があり，RFTが1.0以上の17名中3名でGH分泌刺激試験の反応が低下しており，頭蓋照射を受けたALL経験者に対するGH分泌刺激試験の結果は最終身長を反映していなかった．

Abstract　We investigated factors that affected final height and the response to a growth hormone (GH) provocation test in survivors of childhood acute lymphoblastic leukemia (ALL) who underwent cranial irradiation (CRI). Medical records of 51 patients (33 males, 18 females) who had undergone treatment for childhood ALL were retrospectively examined. Though the expected final height is based on parental height (target height), which is determined by genetic predisposition, we analyzed final height using the height standard deviation score (HSDS) and by calculating the ratio of final height to target height (RFT). HSDS values were within the normal distribution (between −2 and +2 standard deviations) in 46 of 51 patients. The RFT of 3 male and 4 female survivors (13.7%) was below 0.95, and that of 6 male and 8 female survivors (27.5%) was below 0.975. RFT was associated with age at diagnosis and cumulative doses of corticosteroid therapy but not associated with gender or dose of cranial irradiation. Eleven of 12 survivors with RFT < 0.975 showed a normal response to the GH provocation test, whereas 3 of 17 survivors with RFT ≧1.0 showed a low response to GH provocation tests. Thus, there was no relationship between the results of the GH provocation test and final height.

Key words: leukemia, growth hormone provocation test, final height, target height, cranial irradiation

I. Introduction

Survival rates of children with acute lymphoblastic leukemia (ALL) have improved more than 70% over the last two decades.[1-3] Changes in therapeutic methods, such as diagnostic technology, chemotherapy, radiation, and stem cell transplantation, have contributed to improved survival rates. Maintaining a good

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quality of life among survivors who have undergone therapy is the next challenge.

Central nervous system involvement among subjects with ALL has remarkably improved since the introduction of prophylactic cranial irradiation (CRI) therapy. Although CRI therapy has significantly improved the survival rate in children with ALL, late effects such as growth retardation, pituitary dysfunction, and secondary brain tumors resulting from CRI are factors that need to be addressed.[4-7]

Data regarding the adverse effects of therapy on the growth of children with leukemia are conflicting, and numerous factors other than CRI may affect patients who have undergone treatment for childhood leukemia. One matter of concern is how therapy may affect the final height of ALL survivors. In general, final height is evaluated by the height standard deviation score (HSDS), which is determined by comparing actual height with standard heights for the same age group and gender. However, in individual patients the expected final height is based on parental height (i.e., target height), which is determined by genetic predisposition.

The present study examined factors affecting final height and the ratio of final height to target height (RFT) by retrospectively examining growth records, therapeutic regimens, and the results of growth hormone (GH) provocation tests in patients with ALL who had undergone CRI and who survived to reach final height in adulthood.

II. Materials and Methods

We investigated the medical records of 51 patients (33 males, 18 females) who had undergone treatment for childhood ALL between July 1, 1978, and August 31, 1999, at our hospital and who had reached ≥ 5 years of event-free survival.

All survivors remained in first remission and none had received bone marrow transplantation. Fifty survivors had received CRI therapy with 12 to 24 Gy (mean, 20.5 Gy), and 1 survivor had received 30.5 Gy. None had received GH replacement therapy.

Before the 1980s, our institution treated ALL using vincristine, prednisolone L-asparaginase, and CRI as induction therapy, followed by intensive therapy with cyclophosphamide and methotrexate, as well as mercaptopurine and methotrexate for maintenance therapy. Since 1981, all patients have been treated in accordance with the protocols outlined by the Tokyo Children's Cancer Study Group.[1]

Growth records, radiation dosage, cumulative corticosteroid doses, duration of corticosteroid administration, results of a GH provocation test, parents' heights, and clinical details of each patient were obtained from medical records. The height of all survivors was measured every 6 or 12 months from diagnosis to final height. The age of 18 was considered appropriate for measuring final height because growth rates slow to <1 cm/year at this time, indicating that growth has reached a plateau. When investigating growth records, we considered four height values at the following time points: at diagnosis, at the end of intensive therapy, at the completion of all therapy, and final height (18 years).

HSDS were defined as the difference between the height of each patient and that of age-matched standard heights for Japanese children as of 1990.[8,9]

Target height was calculated in centimeters using the following formulae:

$$\text{Target height}_{\text{male}} = (\text{father's height} + \text{mother's height} + 13)/2$$

$$\text{Target height}_{\text{female}} = (\text{father's height} + \text{mother's height} - 13)/2$$

The RFT was also calculated to evaluate the influence of congenital factors. We classified patients into two groups: RFT <0.975 and RFT ≥ 0.975.

To evaluate the influence of corticosteroid therapy on final height, we examined cumulative doses of corticosteroid therapy from the clinical records of all patients. Each treatment consisted of either one or two types of corticosteroid therapy (prednisolone, dexamethasone, methylprednisolone, hydrocortisone, and betamethasone). When the comparison of total dosage was done, the dosage of corticosteroid was converted to prednisolone (mg/m^2) using the following conversion expression, as described by Shigel.[10]

Total dose of prednisolone (mg/m^2)
$=$ prednisolone $\times 1$ + dexamethasone $\times 5/0.75$
+ methylprednisolone $\times 5/4$ + hydrocortisone
$\times 5/20$ + betamethasone $\times 5/0.6$

GH provocation tests were administered one to four times after the completion of all therapy. Provocation tests included propranolol and exercise stimulation,[11] growth hormone releasing hormone (GHRH) stimulation,[12] clonidine stimulation,[13] and sleep studies.[12] Subjects with peak GH levels ≥ 15 ng/ml on propranolol and exercise stimulation, ≥ 10 ng/ml on GHRH stimulation, and ≥ 10 ng/ml on clonidine stimulation provocation tests were considered to have normal GH secretion. For sleep studies, an average GH value ≥ 5 ng/ml was considered normal. Regardless of the number of trials, we considered GH to have been secreted if more than one result of a provocation test showed normal GH secretion.

Statistical analysis

The Student's *t* test was used to compare the HSDS and final height. The crude and adjusted effects on RFT of gender, age at diagnosis, dose of CRI, cumulative doses of corticosteroid therapy, and HSDS at diagnosis were estimated using logistic regression, and results were described as odds ratios and 95% confidence intervals. Relationships between RFT and results of GH provocation tests were evaluated using the Student's *t* test. A p value <0.05 was considered statistically significant. All analyses were performed with SPSS, Advanced Statistics Release 6.0 (SPSS Inc., Chicago, IL, USA).

III. Results

The 51 survivors comprised 33 males and 18 females. Age at diagnosis, age at CRI, dose of CRI, cumulative dose of corticosteroid therapy, and duration of corticosteroid administration were not significantly different between males and females (Table 1). Mean cumulative corticosteroid dose for the 51 survivors was 7,828.3 mg/m^2 (range, 2,450 to 22,625 mg/m^2) prednisolone-equivalents. The mean duration of corticosteroid administration was 158.1 days (range, 73 to 334 days).

The final HSDS values were within the normal distribution in 46 of 51 patients, ranging between -2 and $+2$ standard deviations (SD). The mean final HSDS of all survivors was -0.543 (males, -0.291; females, -1.003). The final HSDS values of 17, 9, and 4 survivors were from 0 to -1, -1 to -2, and -2 to -3, respectively. Only one value was below -3 SD. Five survivors (9.8%; 1 male and 4 females) had values that were below -2 SD, indicating short stature.

The mean RFT was 0.989 in all survivors (males, 0.997; females, 0.975). The RFT of 3 male and 4 female survivors (13.7%) was below 0.95, and that of 6 male and 8 female survivors (27.5%) was below 0.975.

Table 2 shows that HSDS did not significantly differ between time of diagnosis and two other measurement points during treatment, but that values of final height and height at diagnosis differed significantly in all survivors ($p<0.001$). This difference was signifi-

Table 1 Characteristics of survivors

	All (n=51)	Males (n=33)	Females (n=18)
Age at diagnosis			
Mean (yr)	6.02	6.85	4.48
Range (yr)	0.58–14.92	0.58–14.92	0.73–8.58
Age at CRI			
Mean (yr)	6.36	7.18	4.85
Range (yr)	1.67–15.67	2.42–15.67	1.67–10.17
Target dose of CRI			
Mean (Gy)	20.5	20.4	21.0
Range (Gy)	18–30.5	18–30.5	18–24
Cumulative PSL dose			
Mean (mg)	7,828.3	8166.0	7227.9
Range (mg)	2,450–22,625	3,530–22,625	2,450–8,050
Duration of PSL administration			
Mean (days)	158.1	165.9	154.0
Range (days)	73–334	73–334	84–188

yr: years old, CRI: cranial irradiation, PSL: prednisolone.

Table 2 HSDS at four points and RFT

	All (n=51)	Males (n=33)	Females (n=18)
HSDS at diagnosis	0.198	0.279	0.006
HSDS at end of intensive therapy	−0.223	−0.081	−0.484
HSDS at completion of all therapy	−0.212	−0.092	−0.431
HSDS at final height	−0.543*	−0.291**	−1.003*
RFT	0.989	0.997	0.975

HSDS: height standard deviation score, RFT: ratio of final height and target height, *: p-value between at diagnosis and final height was less than 0.001, **: p-value between at diagnosis and final height was 0.019.

cant for both males ($p=0.019$) and females ($p<0.001$).

We compared HSDS at four points between the two RFT groups (RFT$<$0.975 and RFT$\geq$0.975). Table 3 shows that HSDS of final height and RFT significantly differed between these two groups ($p<0.001$ for both comparisons). Age at diagnosis was 3.79 and 6.86 years in the two groups, respectively ($p=0.013$). Age at diagnosis of 14 survivors (6 males and 8 females) with RFT$<$0.975 was younger than 5 years. We also compared the HSDS at diagnosis and HSDS at the end of intensive therapy, HSDS at the end of intensive therapy and HSDS at completion of therapy, and HSDS at completion of therapy and final height in each group. In the group with a shorter final height (RFT$<$0.975), growth tended to be particularly slow during the interval from the completion of therapy to the attainment of final height ($p<0.001$).

In the multivariate model, the odds ratios of age at diagnosis and cumulative doses of prednisolone therapy was more than 1.0. Thus, RFT was positively associated with age at diagnosis, and cumulative doses of prednisolone therapy but negatively associated with gender and dose of CRI. The odds ratio of HSDS at diagnosis was 2.428 but this value was not statistically significant ($p=0.185$) (Table 4).

The GH provocation test was administered once to 24 survivors (15 males and 9 females), twice to 9 survivors (6 males and 3 females), three times to 8 survivors (5 males and 3 females), and four times to 1 survivor (1 male) after completion of all therapy. In total, the 42 survivors underwent 70 tests. The relationship between RFT and the results of the GH provocation tests did not differ significantly (Fig. 1). Only one female survivor of 12 survivors (6 males and 6 females) with an RFT$<$0.975 showed a low response to the GH provocation test. Eleven survivors with RFT$<$0.975 showed a normal response to the

Table 3 Comparison of HSDS and RFT for 2 groups (divided by RFT of 0.975)

	All ($n=51$)	RFT$<$0.975 ($n=14$)	RFT $\geqq$ 0.975 ($n=37$)	p-value
Gender (male: female)	33:18	6:8	27:10	0.04
Age at diagnosis (yr)	6.02	3.79	6.86	0.013
Hegiht at diagnosis (cm)	111.8	95.3	118.0	0.01
HSDS at diagnosis	0.198	−0.221	0.3	0.016
HSDS at end of intensive therapy	−0.223	−0.708	−0.044	0.026
HSDS at completion of therapy	−0.212	−0.492	−0.112	0.272
HSDS at final height	−0.543	−1.531	−0.17	$<$0.001
RFT	0.989	0.948	1.005	$<$0.001

yr: years old, HSDS: height standard deviation score, RFT: ratio of final height and target height, p-value: the results of comparison between RFT$<$0.972 and RFT$\geqq$0.975.

Table 4 Logistic regression anlysis of factors influencing RFT

	95%CI	Odds ratios	p-value
Gender	0.070-1.769	0.352	0.205
Age at diagnosis	1.026-1.886	1.391	0.034
Dose of CRI	0.749-1.199	0.948	0.655
Cumulative dose of PSL	1.000-1.001	1.001	0.022
HSDS at diagnosis	0.655-8.999	2.428	0.185

RFT: ratio of final height and target height, CRI: cranial irradiation, PSL: prednisolone, HSDS: height standard deviation score, CI: confidence interval.

Table 5 Results of GH provocation tests in 2 groups (those with RFT$<$0.975 and those with RFT$\geqq$0.975)

	Stimulator	P & E ($n=24$)	GHRH ($n=31$)	Clonidine ($n=31$)	Sleep ($n=25$)
RFT$<$0.975	Normal response	4	7	6 (2)	8
	Low response	2	1	4	1
RFT$\geqq$0.975	Normal response	12 (3)	19 (1)	10 (1)	10
	Low response	6	4	11	6

P & E: propranolol and exercise, GHRH: growth hormone releasing hormone. Numbers in parentheses refer to the number of survivors who showed different responses to the GH provocation tests each time.

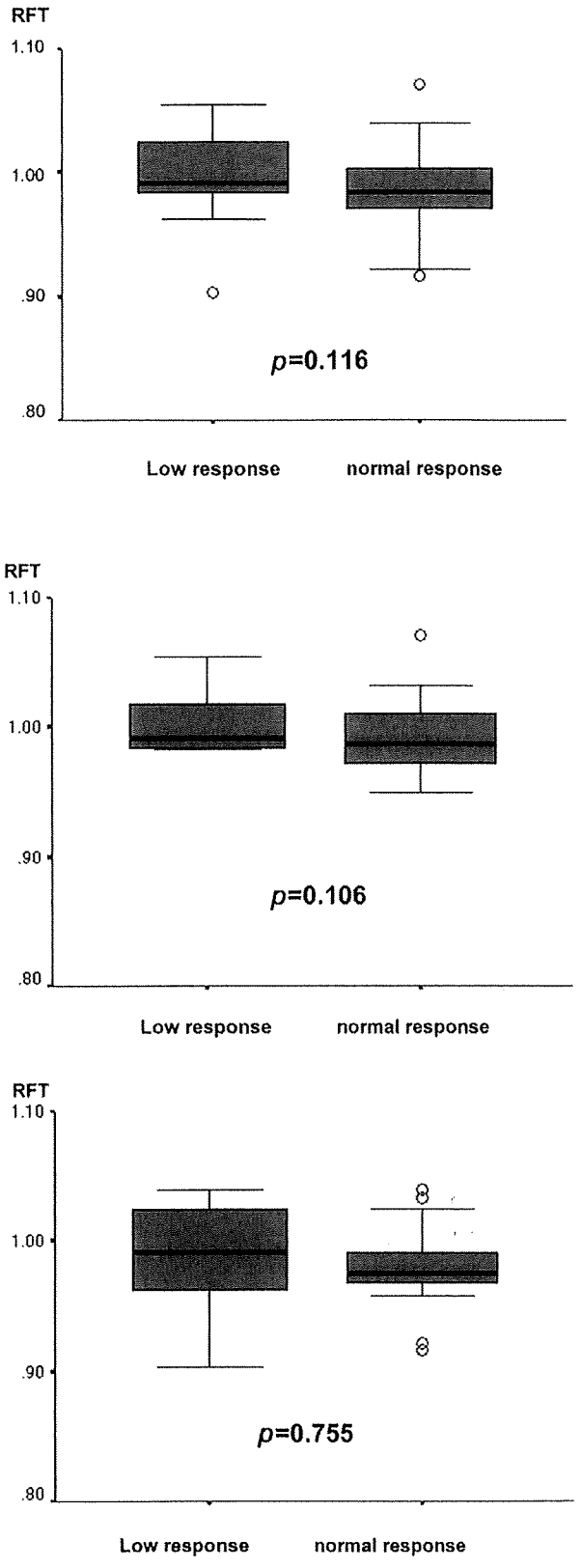

Fig. 1 The relationship between the ratio of final height to target height (RFT) and the results of provocation tests
Top: all survivors, middle: male survivors, bottom: female survivors. Box indicates 10th and 90th percentile, line in middle (bold) indicates median RFT.

GH provocation test. Seven (5 males and 2 females) of 30 survivors (21 males and 9 females) with RFT $\geqq 0.975$ showed a low response to GH provocation tests. Among 4 of these 7 survivors with RFT $\geqq 0.975$ who underwent two to four GH provocation tests, a low response was seen on all tests. Moreover, 3 (2 males and 1 female) of 17 survivors (13 males and 4 females) had a final height that exceeded the target height (RFT $\geqq 1.0$), although they showed a low response to GH provocation tests. Thus, there was no relationship between results of the GH provocation tests and final height.

Table 5 shows the results of GH provocation tests in survivors with RFT < 0.975 and those with RFT $\geqq 0.975$ based on positive or negative responses to different stimulators (i.e., propranolol with exercise stimulation, GHRH stimulation, clonidine stimulation, and sleep). There were no significant differences between survivors with RFT < 0.975 and those with RFT $\geqq 0.975$ despite responses to different stimulators. Eighteen survivors were administered GH provocation tests more than 2 times. Three survivors with propranolol and exercise stimulation, 1 survivor with GHRH stimulation, and 3 survivors with clonidine stimulation showed different responses to each provocation test.

IV. Discussion

The number of reports describing the late effects of leukemia treatment has increased along with improvements in patient prognosis.[14-16] Late effects include several disorders, among which, growth failure is one of the most significant. The reason for short final height in survivors with leukemia who undergo stem cell transplantation (SCT) is due to total body irradiation, using busulfan, or total cumulative doses of corticosteroid therapy. Among survivors who do not undergo SCT, impaired gains in height after treatment for leukemia are presumed to be associated with CRI, which is given to prevent central nervous involvement. However, in most cases, the reduction in final height is only moderate, and most survivors do not receive GH replacement therapy. Kirk et al. followed up patients with childhood leukemia for 6 years after onset and reported that their HSDS was 1.37 lower than the mean and that 71% of subjects were shorter than the standard height by 1 SD or more.[17] In addition, Clayton et al. reported that patients with ALL who were treated for 10 years were significantly shorter than the standard adult height.[18] We examined which factors affected final height in survivors of childhood ALL who underwent CRI but not SCT.

The final height was less than -2 SD in 5 (1 male

and 4 females) of the 51 survivors (9.8%) in the present study, which is approximately 4-fold that of the value reported in the Japanese statistics (2.3%; 2,275/100,000).[19] The final height evaluated by HSDS was −0.543 for survivors overall, −0.291 for males, and −1.003 for females. A comparison of HSDS at diagnosis and at the attainment of final height revealed decreases of −0.741, −0.54, and −1.009 among the overall, male, and female survivors, respectively. These results indicate that the therapy affected final height more in females than in males. Both male and female survivors grew slowly during intensive therapy, but the attenuation of growth during the interval between the end of treatment and the attainment of final height tended to be worse in females than in males. The influence of CRI for leukemia on height has been assessed from the viewpoint of total dose of CRI[20] and age at the start of treatment.[14] However, height is also inherited from parents. Thus we assessed final height using RFT and not HSDS, which is obtained from standard height values, to determine the degree to which final height corresponded to the estimated height based on the height of the parents.

Final height evaluated by RFT was 0.989 for survivors overall, 0.997 for males, and 0.975 for females. These results indicate that therapy did not obviously influence growth in males, but might affect the growth of females. However, the mean age at disease diagnosis was 4.48 and 6.85 years in females and males, respectively ($p=0.086$), indicating that the variance in the influence of treatment could be ascribed to differences in age at time of diagnosis between the two genders.

The age at diagnosis was lower in the group with RFT$<$0.975. All survivors received CRI within 1 year of diagnosis, meaning that they were young when they received this treatment.

In the group with the shorter final height (RFT$<$0.975), growth tended to be particularly slow during the interval from the end of treatment to the attainment of final height. Although the reason for this finding is unclear, it appears that the survivors who had a shorter final height could not catch up any lost growth in this interval.

Some investigators have maintained that reduced final height is mainly related to the total dose of CRI,[21] whereas others disagree.[22,23] Some reports describe reduced final height in patients with brain tumors exposed to high doses of CRI.[24-26] Our results indicate that age at diagnosis and cumulative doses of corticosteroids were related to final height, whereas the total dose of CRI was not.

Some reports have shown that a reduced final height is related to decreased GH secretion in treated survivors of childhood leukemia and that such decreased GH secretion, when recognized early and treated with GH replacement at the end of anti-leukemic therapy, results in favorable growth.[27] We retrospectively investigated results of GH provocation tests in survivors of childhood leukemia. According to the era in which the treatment was applied, one to four types of GH provocations tests, alone or in combination, were used. When the result of at least one test was positive, the GH provocation test was determined to be positive. Figure 1 shows that there were no significant associations between final height and the results of GH provocation tests.

The results of a comparison of GH provocation tests completed 1 month to 4.1 years after the completion of therapy did not reveal any significant relationship between test results and final height at any of the periods examined (data not shown). Similarly, we could not find significant stimulators to GH provocation tests to assess of GH insufficiency in survivors of childhood ALL who underwent cranial irradiation, as shown in Table 5.

Although GH secretion levels during intensive therapy have not been reported, growth is clearly delayed during this period. However, height later recovers and GH secretion is frequently recognized in GH provocation tests, even in patients whose final height is short. Although many survivors can receive GH replacement therapy, some survivors who received CRI and whose final height was short may not have received GH replacement therapy because of their normal response to GH provocation tests. It is possible that CRI and chemotherapy do not lead to a dysfunction in GH secretion, but rather to damage to GH receptors. Additional studies are needed on how to evaluate GH secretion among survivors who receive CRI.

V. Conclusion

We investigated final height after treatment and results of the GH provocation test in survivors of childhood ALL. Age at diagnosis and cumulative dose of corticosteroid therapy affected the final height in survivors with childhood ALL who received CRI. The results of GH provocations test did not correlate with the final height of the survivors. We conclude that the final height of childhood ALL survivors treated with CRI is difficult to predict based on results of GH provocation tests.

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—Review—

Late Effects of Childhood Cancer: Life-threatening Issues

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Abstract

Improvements in therapies for childhood cancers have increased the number of survivors. However, with this prolonged survival, the late effects of disease and anti-cancer therapy are becoming increasingly important. Approximately two-thirds of survivors of childhood cancer will have at least one late effect, and about one-third will have a late effect that is severe or life-threatening. A second neoplasm is one of the most severe late effects in survivors of childhood cancer. Compared with normal populations, persons with a history of childhood cancer have a 10- to 20-fold greater risk of a second malignant neoplasm. Patients who have undergone radiation therapy or been given specific chemotherapeutic agents and patients with a known genetic predisposition to malignancy have been shown to be at higher risk for a second malignant neoplasm. Cardiac problems are another serious late effect for survivors of childhood cancer. Anthracycline-induced cardiotoxicities are common in these patients. A cumulative dose of anthracycline greater than 300 mg/m^2 is associated with an 11-fold higher risk of clinical heart failure compared with a cumulative dose of less than 300 mg/m^2. Serial monitoring of cardiac functioning in children receiving anthracycline allows early identification of cardiac damage. One cardioprotectant (dexrazoxane) has proven effective in adult patients, but larger trials are needed to determine its efficacy in children. It is important to recognize that it may not be best to categorize surviving patients by primary diagnosis. Instead, strategies for surveillance of survivors should be based on the treatment each patient received.

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Key words: late effects, childhood cancer, survivors of childhood cancer, second neoplasm, cardiotoxicity

Introduction

Dramatic advances have been made in the treatment of childhood cancer in the last three decades. The survival rate for children with cancer is now about 80%[1], and more than 0.1% of young adults are survivors of childhood cancer. As the survival rates for childhood cancer have been improving, the late effects of cancer therapy have become a significant problem. To varying degrees, adverse outcomes, including second neoplasms, cardiac dysfunction, pulmonary dysfunction, neurocognitive dysfunction, impaired intellectual function, various endocrine problems, gonadal dysfunction, decreased fertility, and reduced growth **(Table 1)**, have been shown to be more likely in long-term survivors. Late mortality in 5-year

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Table 1 Major physical late effects of childhood cancer

Category	Late effects
Second malignant neoplasm (SMN)	Second leukemia
	SMN in radiation field (brain, skin, bone, soft tissure, breast, thyroid)
Cardiac	Cardiomyopathy
	Valvular disease
	Pericardial complications
Pulmonary	Pulmonary fibrosis
Neuropathy	Neurocognitive deficit
	Leukoencephalopathy
Endocrine	Hypothyroidism
	Hyperthyroidism
	Growth hormone deficiency
	Adrenal insufficiency
Gonadal function	Gonadal failure
	Premature menopause
	Infertility
Growth	Short stature (Growth hormone deficiency. bone atrophy, etc)
Bone	Scoliosis
	Osteoporosis
	Avascular necrosis
Liver	Heepatitis B
	Heepatitis C
Ear	Hearing loss
Teeth	Deantal abnormalities

survivors of childhood cancer is 10.8 times higher than that in the general population[2]. Although the most common cause of death is relapse, late sequelae of treatment of the original disease also contribute to later mortality in survivors of childhood cancer.

Two life-threatening late effects of childhood cancer treatment are reviewed in this article: secondary neoplasm and cardiotoxicity.

Second Neoplasm

Second malignant neoplasm (SMN) is a severe late effect in survivors of childhood cancer. The Childhood Cancer Survivors Study (CCSS), a large cohort study of survivors of childhood cancer, has reported that the cumulative incidence of SMN 20 years after the original cancer diagnosis is 3.2% overall and varies by diagnostic subgroup: 7.6% in Hodgkin disease, 4.0% in soft-tissue sarcoma, 3.3% in bone sarcoma, 2.1% in leukemia, 2.1% in central nervous system cancer, 1.9% in neuroblastoma, and 1.6% in kidney tumor[3]. Compared with persons in the general population, persons with a history of childhood cancer have a 10- to 20-fold greater risk of a SMN[4]. Independent risk factors for SMN (adjusted for radiation exposure) include female sex, original cancer diagnosed at a younger age, original diagnosis of Hodgkin's lymphoma or soft tissue sarcoma, and exposure to alkylating agents[3]. The second adult-type carcinoma occurred at a median of 27 years (range, 10–44 years), and the median elapsed time between the development of the second carcinoma and primary therapy was 15 years (range, 6–28 years)[5].

Radiation therapy is a major cause of SMN[6]. Eighty to ninety percent of SMNs following radiation therapy occur within the radiation field. Breast cancer is the most frequent SMN in female survivors of Hodgkin's lymphoma. This represents a 57-fold risk compared with that in the general population. An increased risk of breast cancer is present in patients who have received more than 40 Gy to the chest, with a notable dose-response relationship. The risk of skin cancer also increases following radiation exposure. Basal cell carcinoma is the most commonly observed subsequent cancer. Forty-six percent of patients with secondary skin cancer have multiple occurrences: 90% have received radiation, and 90% of the cancers are within the radiation field[7]. Radiation therapy is associated with a 6.3-fold higher risk of skin cancer. Thyroid cancer may develop after irradiation of the head, neck, or chest. Papillary carcinoma accounts for 75% to 90% of all radiation-induced thyroid cancers. The incidence of thyroid cancer increases linearly with the dose of radiation but reaches a plateau with doses greater than 30 Gy[8]. This finding may be due to high-dose radiation inhibiting cellular proliferation and preventing the development of an expanded malignant clone. Bone and soft tissue sarcoma may occur after radiation therapy, and the risk is proportional to the dose and the concurrent use of alkylating agents. The British Childhood Survivor of Cancer Study has reported that the overall cumulative risk in a cohort of patients

treated from 1940 through 1983 was approximately 1% within a 20-year period following the original diagnosis[9].

Treatment-related leukemia and myelodysplastic syndrome may be caused by topoisomerase II inhibitors[10] and alkylating agents[11]. The cumulative risk for second leukemia after treatment with a topoisomerase II inhibitor is 0.5% to 18.4%, and the median latency period is 1 to 3 years (range, 0.5–4.5 years)[10]. There is usually rearrangement involving the *MLL* gene on chromosome band 11q23. Recently, Relling et al have reported that short-term use of granulocyte colony-stimulating factor after etoposide therapy might increase the risk of acute myeloid leukemia or myelodysplastic syndrome[12]. Secondary leukemias are also associated with alkylating agents. The cumulative risk for secondary leukemia after treatment with alkylating agents is 0.8% to 2.8%, and the median latency period is 4 to 6 years (range, 1–20 years)[11]. Alkylating-agent-related secondary leukemia is generally associated with abnormalities, usually deletions of chromosome 5 or 7[6].

Secondary brain tumors have been reported to occur with increased frequency in patients who have undergone cranial irradiation for brain tumors or acute lymphoblastic leukemia. A 10-fold or greater risk for brain tumors has been observed for survivors of cancers of the central nervous system (CNS) than for persons who have not had cancer. The CCSS has found that 116 subsequent CNS neoplasms in 14,361 5-year survivors of childhood cancer and glioma occurred at a median of 9 years after the original diagnosis and that meningioma occurred at a median of 17 years after the original diagnosis[13]. The cumulative risk of secondary CNS neoplasms is 0.5% to 2.0% at 20 years. Younger age at initial therapy is a risk factor for secondary CNS malignancies. Other potential risk factors for secondary CNS malignancies are an inherited genetic predisposition to cancer and genetic polymorphisms of metabolic enzymes. An example of a polymorphism that has been found to be predictive of the risk of second CNS tumors in childhood acute lymphoblastic leukemia is thiopurine S-methyl-transferase[14].

Stem cell transplantation (SCT) is another cause of second malignancies. The overall cumulative incidence of developing posttransplant malignancies is 6.9% at 20 years and increases by 2% with each successive 5-year follow-up period[15]. The CCSS has reported that patients who have undergone SCT had a 3-fold increased risk of posttransplant malignancies during 7-year periods[13]. Children younger than 10 years at the time of SCT have a greater risk than do older children[16].

Cardiotoxicity

Cardiologic problems are serious late effects in survivors of childhood cancer. Chief among these late adverse effects is the cardiotoxicity associated with anthracycline therapy. Valvular disease, pericardial disease, and arrhythmias have been reported as late cardiologic effects in cancer survivors. After anthracycline therapy, the risk of congestive heart failure is 0% to 16%, and that of subclinical cardiomyopathy is 0% to 57%. There are two kinds of anthracycline-induced cardiotoxicity: acute and chronic. In some cases, chronic cardiotoxicity is subdivided into two addition types: early and late (i.e., more than 1 year after completion of therapy). Most cases of acute cardiotoxicity are not severe. The incidence of anthracycline-induced chronic cardiomyopathy depends on the cumulative dose of anthracycline. A cumulative dose of anthracycline greater than 300 mg/m^2 is associated with an 11-fold higher risk of clinical heart failure than is a cumulative dose of less than 300 mg/m^2[17]. Steinherz et al have reported that 23% of 201 patients who have received a median cumulative dose of doxorubicin of 450 mg/m^2 have echocardiographic abnormalities at a median interval of 7 years after the completion of therapy[18]. An increased risk of cardiac abnormalities is associated with the cumulative dose of anthracycline, the length of follow-up, and mediastinal irradiation. Moreover, girls appear to be more likely than are boys to have cardiotoxic effects of anthracycline therapy[19]. Although the reason for this difference is not known, differences in sex-specific body fat percentages may be involved. In addition, patients younger than 4 years at the time of anthracycline