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ACUTE AND LONG-TERM NEURODEVELOPMENTAL OUTCOMES IN CHILDREN FOLLOWING BONE MARROW TRANSPLANTATION

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1. ABSTRACT

Bone marrow transplantation offers a potential cure for a number of childhood cancers, sickle cell anemia, and stabilization of a deteriorating and debilitating process in a number of metabolic disorders and leukodystrophies. Depending upon the disease, treatment prior to BMT, and natural history of the disease, BMT may increase the risk of neuropsychological toxicity for children undergoing BMT, or may actually improve their long-term neurodevelopmental outlook. The role of factors such as pre-BMT therapy, age at time of treatment, presence or absence of total body irradiation, and toxicities associated with GVHD are presented for consideration. A developmental model for understanding the emergence of neurocognitive effects of BMT is reviewed, and strategies for intervention are considered.

2. INTRODUCTION

Over the past 15 years, bone marrow transplantation (BMT) has rapidly emerged as the treatment of choice for high risk or relapsed leukemia, and a preferred treatment for a number of solid tumors using peripheral stem cell or autologous rescue procedures (1). In addition, its applications have expanded beyond the oncologic diseases to other hematologic (e.g., aplastic anemia, sickle cell anemia) and immunologic disorders (e.g., autoimmune deficiencies, SCIDS) (2,3). In addition, BMT may represent significant hope in arresting the neurodevelopmental devastation accompanying a number of genetic and metabolic degenerative disorders (e.g., Hurler's syndrome, leukodystrophies) (4-6). While BMT offers a potential cure for these serious and often life-threatening diseases, it may also result in significant long-term morbidity that cannot be predicted with certainty. Alternatively, it may offer the benefit of preventing non-life-threatening consequences of a disease process that substantially affects quality of life. These risks and benefits are determined both by the nature of the underlying disease and the type of procedure used in performing the BMT. The identification of neurodevelopmental risks and benefits of BMT is still in its research infancy, with only minimal data available. However, there are a number of known risk factors for neurodevelopmental problems in children treated with BMT that are related to their underlying disease or prior treatment. This article will focus on known risk factors, considering how they may affect neurodevelopmental outcomes in children treated with BMT.

3. DISCUSSION

3.1. Risk and Benefits of BMT for Children

Bone marrow transplantation offers the potential for successful treatment and possible cure of serious, life-threatening diseases, particularly for children with malignancies. For other children, BMT may be successful in halting a deteriorating, progressive condition resulting in significant developmental delay and motor impairment. For still others, BMT may offer the only opportunity to cure an underlying genetic disease and prevent some of the significant symptoms associated with progression of the disease. On the other hand, BMT is not without risk. Acute mortality related to the procedure varies from estimates of 10 percent to as high as 50 percent, depending

upon the reason for transplantation (1,7). For those children who survive, there is an increased risk of cognitive delays, growth delays, and endocrine problems depending upon the type of transplant and preparatory regimen used (1). For children receiving allogeneic transplantation, the development of a secondary, serious chronic illness, graft vs. host disease, may result in significant isolation, school absence, and reduced quality of life (6,8,9). Finally, due to the isolation often required during and following BMT, these children are at significant risk for long-term social isolation and social skills problems.

3.1.1. Risk Factors for Neurodevelomental Problems

In addition to these treatment related difficulties, a number of other non-BMT risk factors must be considered when evaluating neurodevelopmental outcomes. Children with a family history of neurodevelopmental problems, including mental retardation, attention deficit disorder, or dyslexia may present with poor neurocognitive outcomes for reasons unrelated to their underlying disease, treatment, or BMT. Other major demographic factors, such as poverty, malnutrition, low maternal education, and poor environmental stimulation, are adversely related to neurodevelopment, and these factors may interact with aspects of BMT in unknown ways. Finally, congenital or sensory disorders, such as deafness, birth anoxia, or closed head injury may also contribute to poor neurodevelopmental outcomes in transplant patients.

More specific to BMT, there are a number of disease and treatment factors that increase the risk of neurodevelopmental problems following BMT. For children treated for acute leukemia and other malignancies that involve treatment of the central nervous system, including both chemotherapy and radiation therapy, significant risk for neurodevelopmental deficits exists prior to transplant (6;10). Aspects of the disease process may also significantly increase the risk for later neurodevelopmental problems, particularly for children with sickle cell anemia, where stroke risk is high, and for children with genetic and metabolic diseases associated with progressive deterioration of cognitive functioning. In addition, components of the transplant procedure, including the type of preparatory regimen (e.g. total body irradiation vs. chemotherapy), acute transplant-related problems (e.g., central nervous system infection), or consequences of graft vs. host disease may increase the risk of later neurodevelopmental difficulties for children who are already at risk because of factors associated with their underlying disease.

3.1.2. Disease-Specific Concerns

Evaluation of the risk for neurodevelopmental deficits following transplantation requires an understanding of the underlying disease and treatment approaches associated with different presenting problems. In the following sections, specific concerns related to leukemia, solid tumors, metabolic and degenerative genetic and neurologic disorders, and sickle cell anemia are identified.

3.1.3. Leukemias

BMT is the treatment of choice for children with relapsed acute lymphocytic leukemia (ALL), high risk ALL in first remission (e.g., Philadelphia chromosome positive), chronic myelocytic leukemia, and for some children with acute non-lymphocytic leukemia who have an HLA matched sibling donor (1). For children in the latter two categories (CML and ANLL), pre-BMT risks appear relatively small since they receive minimal treatment of the central nervous system as part of standard therapy.

The risk of neurocognitive deficits in children with ALL who are treated with BMT following a relapse is increased because of prior treatment. Standard treatment for ALL includes central nervous system prophylaxis consisting of intrathecal chemotherapy (methotrexate alone or triple intrathecal chemotherapy-methotrexate, hydrocortisone, ARA-C) and, for some children, 1800-2400 cGy of cranial or craniospinal radiation therapy (11). A number of studies have established a link between poorer neurocognitive functioning and craniospinal radiation (10;12), particularly in combination with intrathecal methotrexate (13). In the mid-1980s, ALL protocols shifted to the use of intrathecal chemotherapy alone for CNS prophylaxis, eliminating craniospinal radiation therapy in the hopes of reducing neuroendocrine and neuropsychological deficits. Unfortunately, subsequent evaluations of children treated on protocols involving only intrathecal chemotherapy suggest that negative outcomes have not been eliminated. In a Pediatric Oncology Group study, Brown and his colleagues found that children treated with triple intrathecal chemotherapy experienced identifiable deficits and neuropsychological and academic functioning three years following diagnosis (14). A subsequent Pediatric Oncology Group protocol included increased doses and frequency of exposure to systemic methotrexate. Approximately 7-10% of the children treated on this protocol developed neurological consequences including seizures, motor tremors, and changes in the white matter detected by neuroimaging (15). These findings support the supposition of risk prior to bone marrow transplantation for children treated on even the most current ALL protocols, and increase the chances that neurocognitive deficits will be found following BMT.

Very few studies have been completed that systematically evaluate neurocognitive outcomes in children who received either autologous or allogeneic BMT. However, the use of total body radiation, cranial radiation for children with central nervous system disease, and the addition of other potentially neurotoxic chemotherapy agents used in preparation regimens may independently or in combination with prior treatment increase the neurocognitive risk for children receiving BMT. Although it is not possible to determine the specific cause or relative contribution of BMT to neurocognitive outcomes, children with ALL remain at significant risk for neurocognitive complications that may emerge over years following completion of BMT.

3.1.4. Solid Tumors

Pre-BMT treatment of solid tumors primarily involves systemic chemotherapy, surgery, and in some cases, local field radiation therapy. For the majority of solid tumors, these treatments are associated with minimal or infrequent cognitive consequences (1). The exceptions

include tumors of the central nervous system, as well as tumors of the face and orbit that require radiation therapy fields that include part of the brain (e.g. rhabdomyosarcomas), lymphomas that are either primary or metastatic to the brain, and tumors that require extended exposure to vincristine, which may affect processing speed and motor abilities, adversely impacting on academic achievement (16).

Tumors of the central nervous system are the second most common type of cancer in children, and there are significant cognitive toxicities associated with brain tumors, their surgical removal, and late effects of chemotherapy and radiation to the brain. Very significant, long-term specific deficits in cognitive functioning may be associated with tumor location, difficulties associated with surgery, and secondary complications (e.g. hydrocephalus) requiring long-term management (12). Children treated with high dose cranial radiation have long been known to be at significant risk for cognitive impairment, with both pervasive and specific deficits being identified. The severity of these deficits has been related to the age of the child at the time of treatment, as well as the overall exposure dose of radiation therapy, with younger age at treatment and higher dose being associated with significantly more severe and pervasive cognitive deficits. In addition, the degree and type of impairment changes and appears to increase over time as new deficits emerge with increasing age (10,12,17,18). Some of these long-term problems may be additionally enhanced through interactions between radiation therapy and specific chemotherapy, particularly cisplatin, This may result in high frequency hearing loss that is subsequently associated with difficulties in language-based learning (12). These disease and treatment factors place children with brain tumors at a significant pre-BMT risk for neurocognitive deficits, and may make determination of the contribution of BMT to neurocognitive functioning difficult, if not impossible. However, it is clear that these children enter the transplant setting with a significant, pre-existing risk for neurocognitive impairment.

3.1.5. Metabolic and Degenerative Neurologic Disorders

Recently, BMT has been applied to a variety of non-malignant conditions, predominantly genetic and metabolic disorders. Most of these disorders have no known cure, and often lead to early death or severe motor and/or neurocognitive impairment, including profound mental retardation. This is particularly true of metabolic disorders, some of the leukodystrophies, and auto-immune deficiency disorders (3,4,19,20). For these disorders, BMT appears to arrest the progression of the degenerative disorder. While BMT is not associated with improvement in prior function, evidence suggests that it may arrest further declines in neurocognitive impairment in diseases like Hurler's Syndrome and metachromatic leukodystrophy, or at least significantly alter the rate of decline (6;19;21-24). Neurodevelopmental outcome appears to be dependent to a large degree upon the level of functioning at the time the child is transplanted. Early BMT appears to be associated with better outcome (19). The major limiting factor to this observation is the developmental level of the child at the time of BMT. Children with developmental functioning in the impaired range at the time of transplant do not appear to benefit to the same degree as children with functioning in the non-impaired range. These children also appear at greater risk to have further developmental declines after BMT (19,22,23). This strategy of early BMT is somewhat different from that taken with children with malignancies, where delays in exposure to toxic regimens are considered important in reducing neurocognitive late effects. For children with metabolic and genetic disorders, the consequences of disease progression appear to far exceed the late effects consequences associated with BMT. Early identification of the disorder and early transplant appear to be associated with better overall outcome, and better specific neurodevelopmental outcome.

3.1.6. Sickle Cell Disease

Sickle cell disease is a genetic disorder affecting approximately one in 400-500 black babies born in the United States each year. Despite the identification of the hemoglobin S gene nearly 40 years ago, treatment of sickle cell disease has not improved substantially during that period. The hallmark feature of sickle cell disease involves occlusion of blood vessels resulting in ischemic tissue and organ damage. A multitude of symptoms may be experienced, including pain episodes, increased risk of bacterial sepsis, acute chest syndrome, growth delays, avascular necrosis, systemic organ damage, and, of significant consequence, stroke (25). Approximately 5-10 percent of children with HbSS disease who are under the age of 15 will experience a clinical stroke, and nearly 25 percent will have either clinical or neuroimaging evidence of a central nervous system infarct (26). These infarcts have been associated with high cerebral artery flow velocity that is detected by transcranial Doppler ultrasonography (27).

Both clinical and silent infarct are associated with deficits in neurocognitive functioning. Clinical infarcts are initially associated with more severe and pervasive neurocognitive deficits, but children with "silent" infarcts (detected by neuroimaging) also experience neurocognitive deficits (26). Further, preliminary findings from the Cooperative Study of Sickle Cell Disease suggest that children with HbSS disease, even those with no evidence of infarct on neuroimaging, experience a decline in neurocognitive functioning over time (28). This is likely associated with damage to the microvascular system, but may also be related to chronic anemia, episodic hypoxia, or poor pulmonary functioning (25).

These significant clinical events have led to the use of BMT as a potential cure for the disease, with notable success. The benefits of BMT, in addition to cure, include the arresting of further neurodevelopmental decline, and prevention of future brain infarct and subsequent neurodevelopmental impairment for these children. However, there are risks associated with BMT in sickle cell disease that must be noted. There is an acute mortality risk of approximately 10 percent with bone marrow transplantation, and this must be balanced against a 10 percent mortality risk due to the disease before age 18. There is no way to determine the specific clinical course for an individual child, so the decision to transplant is based

upon current clinical functioning, and is often reserved for children who have already experienced significant disease-related consequences (2). While studies are underway that include neurocognitive outcome assessment of children treated for sickle cell disease with BMT, the data on outcomes are not yet available. This is an emerging area that will require close observation and careful evaluation as the procedure is made more widely available.

3.1.7. BMT Procedural Factors Associated with Neurocognitive Risk

In addition to pre-BMT disease and treatment factors, there are several aspects of the BMT procedure that should be considered potential risk factors for neurocognitive deficits in children undergoing BMT. For those children treated with allogeneic approaches that include total body radiation as a preparatory regimen, several risk issues should be considered. First, the dose of TBI may be contributing factor. While TBI doses for BMT are substantially lower than those used in treatment of CNS diseases, several investigators have reported worsened neuropsychological functioning following BMT that included TBI (29-31). Others have only identified this pattern in young children, particularly those transplanted under age 3 (8,32,33). However, the combination of TBI with (a) prior treatment of the central nervous system that includes craniospinal radiation, intrathecal chemotherapy, high-dose methotrexate, (b) microvascular damage, or (c) presence of neurodevelopmental delays prior to BMT may also contribute to increased risk for neurodevelopmental problems.

A second significant factor associated with neurocognitive impairment following BMT is the occurrence of acute events during the transplant phase. Perhaps the most concerning of these is central nervous system encephalitis. While relatively rare, these do occur, and in survivors may be associated with severe acute and long-term neurodevelopmental problems. The literature describing the outcomes of children with CNS encephalitis during transplant is essentially nonexistent. However, anecdotal observations suggest that, in children over age four, recovery of language and motor abilities following a CNS encephalitis is possible, depending upon the extent of the injury. However, long-term deficits in attention, memory, fine motor coordination, reading, math, and social functioning may be expected. The pervasiveness and severity of the deficits may be greatly dependent upon the age of the child at the time of the infection.

In rare cases, graft-versus-host disease (GVHD) may affect the central nervous system. However, unless the CNS is involved, GVHD has not been identified as a biologic determinant of neurodevelopmental problems in children receiving BMT. However, severe acute GVHD that requires extended hospitalization or chronic GVHD that results in prolonged restriction of activity may indirectly result in significant educational and social delays (34).

3.2. Neurocognitive Outcomes Following BMT

Research on neurodevelopmental outcomes following BMT is very limited. Preliminary findings suggest that autologous transplantation is not associated with any significant neurodevelopmental problems up to two years following the BMT. The exceptions to this observation seem related to pre-existing neurodevelopmental problems or to acute CNS infectious events. On the other hand, preliminary findings are mixed for allogeneic BMT, particularly for children treated for leukemia. Several investigators report neurocognitive deficits immediately after BMT, or a slow emergence of neurodevelopmental problems, depending upon the preparatory regimen used, the inclusion of TBI, the age of the child at the time of transplant, and the severity of GVHD and other complications (29-32,35-37). Phipps and his colleagues reported impairment only for young children (8). In those studies reporting impairment, the majority involve attentional processes, visual-processing problems, and fine-motor coordination (30,31,35).

On the other hand, BMT appears to have minimal adverse effect for children treated with BMT for non-malignant disease, with stabilization of deteriorating functioning noted in these cases (5,6,19,21-24). Teasing out the impact of BMT on neurodevelopment may be quite difficult. There are a host of diseases being considered for transplant and the variety of different protocols significantly confound the interpretation of BMT outcomes. We know little about the acute toxicities and lasting effects of preparatory regimens and complications during the marrow recovery period. Important non-biologic factors, such as lack of opportunity for learning and practicing skills, may play major roles in neurodevelopmental functioning after transplant. Finally, neurodevelopmental effects may be time dependent, and therefore not detected until years after treatment is completed (8).

3.3. Developmental Considerations

Because children's brains continue to develop into their late 20s, we can expect a systematic emergence of functions that are age dependent over time. For this reason, repeated assessment is needed to determine functional issues for children treated with BMT as they age. Predictions of future difficulties may be able to be made using a developmental model, and if confirmed, should be integrated into a preventive intervention approach (10,17).

There are three courses of neurodevelopment that must be considered for children undergoing BMT. The first is the course associated with genetic metabolic disorders, where steady deterioration and loss of function occurs across time. For these children, BMT may serve to arrest a downward course of progressive disability. The second is the course where development does not deteriorate, but fails to progress. Over time, these children will present with significant developmental impairments, with abilities arrested at the point that development stops. The third is course where the child experiences slow development, as well as the emergence of diminished, specific functional abilities over time. A developmental model suggests that we can anticipate some of these deficits, based on the age of the child at the time the CNS is affected (17).

Early perspectives on neurocognitive deficits in children with cancer, sickle cell anemia, or genetic

developmental disabilities focused heavily on global measures such as intelligence. Recently, increased attention has been paid to deficits in specific functional abilities, not global deficits, and efforts are under way to link these deficits to developmental processes in the children's brains. Common areas of specific concern include deficits in processing speed, attention, memory, and academic difficulties in math and reading. For young children, additional concerns include auditory processing and language development (10,17).

Within each of the specific areas, common patterns emerge. Processing speed is one of the most common areas of deficit, and typically involves a general slowing in the processing of information. Simple repetitive tasks are minimally affected, but the deficit enhances when interpretive tasks are involved and a higher degree of complex information processing is needed. Attentional problems are also very common, although these are often quite different from the types of attention problems seen most commonly in pediatric practices. Attentional problems in these children are often characterized by low rates of hyperactivity and impulsivity, and instead involve higher rates of omission errors, variability in responding, short periods of inattention, and an inability to sustain attention for long periods of time. Likewise, memory problems are specific in nature. Except in young children, memory for verbal information tends to remain intact, with problems noted in memory for visual information, information not presented in a meaningful context, and information presented in sequences. A time delay between stimulation for recall to actual recall, sometimes lasting minutes to hours, is frequently noted. Mathematics skills are often impaired, although the difficulties typically involve basic calculation skills while math concept application skills appear less affected. Reading also emerges as an area of deficit for some children. Early word decoding is not a difficulty, but as the text difficulty increases with increasing age, significant problems with reading may emerge. Children may be taught to recognize words, but comprehension of the information read often declines, having a concurrent affect on reduced vocabulary and acquisition of content information (10,12,17).

3.4. Intervention Strategies

Knowing that children are at risk and identifying problem areas will inevitably require the development of interventions that address neurobehavioral and educational concerns. These strategies include being aware of potential areas of deficit prior to transplantation and making plans for educational support during the transplant and post-transplant periods. School personnel should be informed about anticipated risks, and included in planning for educational support during the transplant period. Following transplant, appropriate placement in home-bound instruction programs, combined with tutorial assistance, is essential to support the child's ongoing learning progress. Once the child is able to return to school, an Individual Education Plan should be developed to address both the identified and anticipated neurodevelopmental problems likely to be encountered.

There are a number of educational modifications that may be appropriate for the child experiencing neurocognitive problems following BMT. For children with visual-spatial-motor problems who develop difficulty with reading, books on tape may be a very effective adaptation that maintains vocabulary and language development, along with new content acquisition. For some children with attentional problems, trials with stimulant medications may be effective (38), but the evidence to support this approach remains limited and consideration should be given to the potential interactive effects of this medication with the disease process and other medications. For children with motor speed and coordination problems, the use of keyboard skills instead of handwriting may prove beneficial, and for older children, the use of voice recognition software to permit dictation may completely circumvent the significant problems encountered in written work. Since math application skills may remain intact while difficulties with calculation skills emerge due to memory deficits, the use of a calculator to support the continued development of math concepts should be strongly considered. Modifications in time demands, especially on standardized testing, will be essential. Other rehabilitative approaches, such as cognitive remediation training using mass practice and computer based training, may also be helpful (39).

It is critical that evaluation and intervention services be monitored across the years following BMT. Experience with the gradual emergence of late effects in children treated for brain tumors, ALL, and sickle cell disease suggests that focusing just on the immediate post-BMT period is inadequate.

4. CONCLUSIONS

BMT may represent the only hope for children with relapsed leukemia, recurrent CNS tumors, or diseases resulting in bone marrow failure. In these cases, the benefits of BMT clearly outweigh any risks related to neurocognitive functioning. For children with metabolic or genetic disorders, BMT may represent an opportunity to arrest a progressive, debilitating disease. In these cases, the neurocognitive risk is minimal, and benefits to protection against further neurocognitive decline may be significant. In sickle cell disease, BMT may represent an opportunity for cure, but the individual nature of the disease, experience with the disease symptoms, and the limited ability to predict outcomes for individual patients increases the need for careful examination of the ethical implications of the use of BMT. Appropriate study of the impact of BMT on the neurodevelopmental course in sickle cell disease is needed.

Much of the information provided in this article is anticipatory and based upon an understanding of the known risks for children with disorders that require BMT. Some research is being conducted that will shed light upon the contribution of BMT to neurocognitive functioning, but solid outcomes are not available at this time. However, it is clear that for some children BMT may represent an additional burden to their neurocognitive development,

while for others, BMT may prevent ongoing deterioration of neurocognitive functioning and worsening quality of life.

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