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Shared Medical Decision-Making: Considering what Options to Present based on an Ethical Analysis of the Treatment of Brain Tumors in Very Young Children

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Abstract

The treatment of brain tumors in very young children poses both a therapeutic challenge and a bioethical quandary. The administration of craniospinal radiation after surgery offers the greatest chance for cure but causes severe neurocognitive damage. As a result, current practice does not offer parents the option of full-dose post-operative craniospinal radiation. Some may regard this approach as inappropriate medical paternalism, while others may consider it an example of responsible therapeutics. Evaluation of this dilemma reveals principles which can guide clinicians in determining which treatment options to present to their patients or surrogates, in the context of shared medical decision-making.

Keywords

ethics; neuro-oncology; pediatric oncology; decision making

Introduction

Shared decision-making has been widely endorsed as the preferred method for making medical decisions. This approach involves clinicians presenting options to their patients, or their patients' surrogates, and helping them choose a treatment plan. (1) The first step in this process, deciding which options to present, can have a significant impact on final treatment decisions, yet has received little attention in the literature. Clinicians clearly should not present options which are ineffective; a more difficult challenge is whether to present treatment options that are effective but also highly toxic. This dilemma is especially germane to pediatric oncology where advances have produced dramatic increases in overall survival (2), yet minimizing therapy related toxicity remains a challenge. This challenge is exemplified by the treatment of brain tumors in very young children, where increases in survival have been accompanied by substantial toxicity. (3)

Brain tumors comprise approximately one quarter of all childhood cancer. (4,5) For certain brain tumors full-dose craniospinal radiation, administered postoperatively, is most likely to result in cure. Yet, the neurocognitive effects are often devastating in very young children. The medical community regards these toxicities as excessive and full-dose radiation

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typically is not offered to the parents of very young children. (3) The implications of this approach are exemplified by the treatment of medulloblastoma in very young children. Due to avoidance of full-dose postoperative radiation, children with medulloblastoma under the age of 3 are less likely to survive compared to older children, (6) despite being more likely to have favorable biological characteristics. (7)

The fact that clinicians do not offer the therapy with the highest curative potential might be regarded as inconsistent with shared decision-making. Some parents might prefer the greater chance for cure, even at the cost of reduced cognition, but this option is typically not offered to them. Evaluation of this practice offers the opportunity to consider what principles clinicians should use when deciding which options to offer patients or surrogates, as part of shared decision-making.

Medulloblastoma

Medulloblastoma is the most common malignant brain tumor of childhood. (7) One third of those affected are under 3 years of age. (8) Treatment involves surgery aimed at gross total resection of the tumor, followed by regimens that include full-dose radiation, modified radiation, or no radiation, as well as chemotherapy. Data on survival and neurocognitive outcomes for these therapeutic regimens are limited in children under age 3. Yet, the existing data, together with extrapolation from data on older children, reveal a conflict between maximizing the chances for long-term survival versus preserving long-term cognitive function.

Full-dose craniospinal radiation

Full-dose postoperative radiation involves craniospinal radiation to a dose of 36 Gy and a boost of 54–59.4 Gy to the posterior fossa. In studies of children over age 3, five-year survival rates following full-dose radiation alone were 50–60% for average-risk disease and 40% for high-risk disease. With the addition of adjuvant chemotherapy, five-year survival rates improved to 85% and 70% respectively. (7) In a recent institutional review, at a median 81 months follow-up medulloblastoma patients under age 3 who were treated with full-dose radiation and chemotherapy exhibited 75% survival. However, these patients had significantly greater neurocognitive deficits than very young children who did not receive full-dose radiation. (8)

The neurocognitive effects of full-dose radiation in very young children were first observed in the 1960's, with reports of severe mental retardation. (9) At 10 year follow-up, a review of children with medulloblastoma across all age groups, the majority of whom were treated with full-dose radiation, found IQs under 80 in 85% and IQs under 60 in 46%. (10) A recently published 6 year follow-up of children over age 3 demonstrated deficits in IQ, knowledge acquisition, reading, processing, memory, and attention among participants. Most striking was the continued loss of cognitive function over time, with an average IQ decline of 2–4.6 points per year. Younger age at cranial irradiation resulted in a steeper decline in IQ (11) suggesting that the degree of cognitive decline is likely to be even greater in children under 3.

The existing data, while limited, suggest that children under age 3 who are treated with full-dose radiation and adjuvant chemotherapy have approximately an 80% chance of survival but will experience significant cognitive decline (Figure). Assuming a decline of approximately 4 points per year, children with an average baseline IQ of 85 will have an IQ in the 60's 5-years following full-dose radiation, and an IQ in the 40's by 10 years. It is unclear whether the cognitive decline would then plateau, or would continue over time. With an IQ in the 40's, the children would have moderate mental retardation, would be unlikely to

live independently or hold a skilled job, and would have significantly impaired relationships with age-matched peers.

Modified Craniospinal Radiation

Due to the observed neurocognitive damage following full-dose radiation, general practice for the past few decades has been to administer reduced doses in young children who receive craniospinal radiation. (12) This approach involves 24 Gy to the craniospinal axis, a 35% reduction from full-dose, with some centers further reducing to 18 Gy. (3) For very young children, these regimens typically begin with chemotherapy in order to delay radiation until the patients are over age 3.

Cure rates for children over age 3, who have average-risk medulloblastoma and receive 24Gy postoperative craniospinal radiation, approach the cure rates for children treated with full-dose radiation. However, attempts to delay radiation have been less successful, especially when the dose of radiation is also reduced. A study of pre-radiation chemotherapy followed by delayed and reduced dose radiation in children over age 3 with average-risk disease showed a progression free survival of 40%. (13) One study of postoperative chemotherapy in very young children followed by delayed full-dose radiation demonstrated a 5-year progression free survival of 21% and overall survival of 51%. (14) Another study of children who received chemotherapy until age 3, followed by reduced dose radiation, found a 5-year progression free survival rate of 34% and an overall survival rate of 45%. (15) For patients with localized disease another approach to limit exposure to radiation has been the use of focal radiation therapy limited to the posterior fossa. A Children's Oncology Group Study of infants with non-metastatic medulloblastoma, treated with neoadjuvant chemotherapy and second surgery, followed by focal radiation with adjuvant chemotherapy, demonstrated event free survival of 58% for those with complete tumor resection at diagnosis. (3)

At 10 year follow-up, a review of children treated with a 10–15% reduction in radiation dose found IQs under 80 in 100% of the children treated before age 3. (10) Another study of very young children with a median baseline IQ of 88 who were treated with postoperative chemotherapy followed by delayed full-dose radiation found an average decline of 3.9 IQ points per year, resulting in a median IQ of 62 at 4.8 years follow-up. (14) A randomized trial of full-dose versus reduced dose radiation in children over age 3 with average-risk medulloblastoma demonstrated that reduced dose radiation resulted in comparative neurocognitive sparing, with a 10–15 point IQ advantage even among the younger participants. (16) In other tumor types, which may be comparable to medulloblastoma, focal radiation has resulted in relative IQ preservation in young children, with deficits in other areas such as reading. (17)

Extrapolation from the available data suggests that children who receive chemotherapy and modified radiation therapy have approximately a 50% chance of survival and a less steep decline in IQ compared to those who receive postoperative full-dose radiation and adjuvant chemotherapy, yielding a projected IQ in the 60's at 10 year follow-up (Figure). These children would have mild mental retardation and, with sufficient support, may be able to live independently, hold a skilled job, and have some age-matched peer interactions.

No Radiation

The degree of observed neurotoxicity has led to radiation avoidance for many very young children with medulloblastoma. (15) A Children's Cancer Group study of children under age 3 who received chemotherapy without radiation, unless there was residual, recurrent or metastatic disease, reported a 5-year event free survival of 32% and overall survival of 43%.

(18) Subsequent histologic review in this study demonstrated 5 year event free survival of 77% and overall survival of 85% for those with desmoplastic histology compared to 17% and 29% respectively in those without. (19) A French cooperative group trial of chemotherapy only in young children demonstrated 5-year progression free survival in 29% of children with fully resected disease, 6% in children with residual disease and 13% in children with metastatic disease. After salvage therapy with high-dose chemotherapy, stem cell rescue and focal irradiation, overall survival rates at 5-years were 73%, 41% and 13% respectively. (20) A German trial of postoperative chemotherapy, administered intraventricularly as well as intravenously, achieved a 5-year progression free survival of 82% in children with completely resected localized disease, 50% in those with residual tumor, and 33% in children with metastatic disease, for a total combined 5-year event free survival of 58%. (21)

The German study's high survival rate may have been influenced by the relatively high proportion of patients with the favorable prognostic feature of desmoplastic histology, over 50%, (22) in contrast to other series where this histology was seen in only 24%. (8) Notably, fewer than 20% of children under age 3 with medulloblastoma are treated on cooperative trials. (22) Results of these studies may therefore be non-representative and survival statistics, especially for high-risk patients, might be well below those reported.

While young children with medulloblastoma have lower than average IQ's at baseline (14) as a result of the implications of the tumor and its surgical removal, those treated without cranial radiation would not be expected to have further cognitive decline over time. Patients in the aforementioned German study were found to have lower IQ's than healthy controls but also demonstrated significantly better general intelligence than children in a previous study who had received craniospinal radiation. (21) The French group reported a mean IQ of 91 in patients treated with chemotherapy alone in contrast to an IQ of 72, at a mean 62 months follow up, in patients who received radiation salvage therapy. (20) Based on the available data, children treated with chemotherapy in the absence of radiation have approximately a 30% chance of survival and an expected average IQ of around 85 (Figure). These children would likely have some special educational needs but would be expected to live independently, hold a skilled job and have unimpaired relationships with age-matched peers.

Discussion

The existing data suggest that the treatment of medulloblastoma in very young children poses a dilemma between survival and preservation of cognitive function (Figure). Current practice does not offer full-dose radiation to children less than 3 years of age, even though this approach has the highest curative potential. While some may consider this practice paternalistic, paternalism in its strict sense represents a violation of the right of an autonomous agent for self-determination and does not apply to very young children. (23) Instead, the question is whether current practice represents a responsible approach to shared decision-making, or involves clinicians inappropriately withholding treatment options. This case highlights the vital role of the first step in the shared decision-making process: which therapeutic options should clinicians offer to patients and surrogates?

Patient's Interests

To determine which treatments are reasonable options for a given patient, clinicians must use the best available evidence to evaluate their risks and potential benefits and evaluate which therapeutic options best promote the patient's interests. (24) For very young children with medulloblastoma it is not immediately clear which option best promotes their interests. Full-dose radiation is associated with greater survival, but significant cognitive deficit;

modified and no radiation regimens are associated with less cognitive toxicity, but lower survival rates.

One way for clinicians to determine which option better promotes individuals' interests is to ask what a reasonable person would choose. Data suggest that the majority of adults would not be willing to accept a significant decline in cognitive function in exchange for a greater chance of cure. (25) The experience for children is not exactly analogous to that of adults, since adults who experience a sudden decrease in cognitive function have to adjust to a level of functioning inferior to that which they had previously attained. This adjustment would likely be very traumatic and necessitate a shift in self-image and way of life.

The experience for children who undergo full-dose radiation, however, may be equally or more traumatic overall. Very young children who undergo full-dose radiation would experience gradual continued cognitive decline over at least a decade. This would make it extremely difficult to attain and sustain milestones of achievement at the very time the child is developing his/her self-image. The child's ability to cope would be hampered by an ever-decreasing aptitude which would likely be accompanied by mounting frustration. (11) Further, the social divide between the child and his/her peers would widen with each passing year. These harms suggest that postoperative full-dose radiation may not be in the interests of very young children, even though it offers the greatest chance for cure.

Patient and Surrogate Role

When it is not clear which options would best promote the patient's interests, a reasonable approach would be to present all the available options to the patient or surrogate. Given that it is not entirely clear whether full-dose postoperative radiation is in the best interests of very young children, clinicians might offer it to the parents amongst the range of options. This approach might be especially appropriate in the context of shared decision-making in pediatrics, given claims that there should be very few limitations on the scope of parental decision-making. Indeed some argue that parents should have the authority to make any decision for their children taking into account the interests of the entire family unit, provided that it is not clearly abusive or neglectful. (26) Others cite the harm principle claiming that interference with parental authority for medical decision-making should be limited to cases in which the parents' choice would "significantly increase the likelihood of serious harm as compared to other options" (27).

While it is important to respect parents' and surrogates' rights to make decisions on behalf of their charges, it also is important to consider the impact of decision-making on the decision-makers themselves. Data reveals that making treatment decisions for others can have a dramatic negative physical and emotional impact which can persist for months to years. (28, 29) One review found that at least one third of surrogates experience prolonged negative emotional effects. (30) Parents may be especially likely to suffer long lasting emotional turmoil as a result of the decisions they make for their children, given that they have to balance the potentially conflicting social, emotional, physical and economic interests of the entire family, and may be further burdened by feeling responsible for the child's eventual outcome.

A study of the parents of children with cancer found that, both at the time of diagnosis and 6 months later, the majority of parents preferred to take a collaborative or passive role in the decision-making process. (31) These data suggest that parents may not wish to bear the burden of critical decision-making in pediatric oncology. A study of shared decision-making in a pediatric population with ADHD demonstrated that the majority of parents felt strongly that they should be fully informed about all treatment options but also tended to prefer a collaborative decision-making process. (32) The potential for significant burden, and

evidence that parents often prefer to share or defer decision-making, suggests that offering parents the seemingly impossible choice of whether to privilege protecting their children's cognitive function or chance for survival may be inconsistent with parents' preferences and may lead to significant harm for the parents.

While some may argue that, absent an expressed desire to defer decision-making, all options should be presented to the parents, the impact on the parents as decision makers seems an important consideration. Further, clinicians should not present unacceptable options to a patient, parent or other medical decision-maker. Thus, in addition to patients' interests and parents' rights, the analysis needs to consider the medical acceptability of the available options and the role of physician responsibility.

Do No Harm

One of the guiding principles of ethical medicine is "to help, or do no harm"(33) but, as in the case of medulloblastoma therapy, the distinction between helpful and harmful can be complicated and the boundaries unclear. To determine which treatment options are appropriate and which cause excessive harm in this context, it is useful to look for analogies in other areas of cancer therapeutics. In drug development, chemotherapy is tested to determine the maximum tolerated dose, that is, the dose at which the drug is deemed too toxic for further escalation. If a drug is nephrotoxic at a specific dose, for example, dosing beyond this level is not pursued, even if higher doses might be more likely to have an anti-tumor effect. Similarly, in clinical practice, cumulative limits are set on chemotherapeutic agents that are known to cause end organ damage such as cardiotoxicity, nephrotoxicity or pulmonary fibrosis. In this way, clinicians avoid causing certain significant organ damage even when the therapy is associated with higher curative potential. This suggests that, according to prevailing practice, destruction of organ function, even in the process of tumor eradication, is regarded as causing excessive harm.

Neuro-cognitive damage seemingly differs from other end organ damage because it does not necessarily lead to death, yet patients can also survive with varying degrees of compromised organ function. For example, end stage renal failure caused by nephrotoxic chemotherapy can be survivable with hemo-dialysis. Nonetheless, clinicians avoid causing renal damage to this degree. The critical distinction is that, in contrast to other organ damage, the boundaries of acceptable loss of neurocognitive function are much less clear.

Limits to cranial radiation can, and should, be defined in order to avoid causing excessive brain damage. While it is not clear where the line should be drawn, there is a degree of loss of cognitive function that represents excessive harm. The neuro-cognitive impairment associated with full-dose craniospinal radiation seems to cross this line. Importantly, this conclusion does not depend on making quality of life determinations for those with IQs of 40. The critical distinction is the difference between an existing state and creation of that state. With regard to chemotherapeutics, for example, no value judgment has been made regarding the quality of life for patients in end stage renal failure. Rather, the field as a whole has determined that it would be irresponsible for clinicians to administer a treatment that will certainly destroy a patient's kidneys. Similarly, one need not make quality of life judgments to assert that administration of a treatment that will certainly cause severe neuro-cognitive disability is excessively harmful and thus medically irresponsible.

In addition, the present choice is not one of cognitive disability or certain death. The alternative treatment options offer a significant, albeit lower, chance of survival. It thus seems medically inappropriate to offer a treatment option which necessarily causes excessive brain damage when there are other options which spare cognition and offer a significant chance of survival.

Conclusion

Treatment of very young children with brain tumors poses an ethical and therapeutic dilemma which provides a platform for evaluating which options clinicians should offer patients and surrogates. Analysis of the present case suggests that, for several reasons, current practice, in which full-dose postoperative craniospinal radiation is not offered to the parents of very young children with medulloblastoma, represents responsible therapeutics. First, although it offers the greatest chance for survival, full-dose radiation may not be in the best interests of very young children. Second, even in an era of shared decision-making, clinicians should take into account the impact of making treatment decisions on parents and surrogates; asking parents to choose whether to privilege their child's survival or cognitive function may lead to significant harm for the parents. Parental and surrogate medical decision-making is also limited such that they may not expose the patient to undue risk for harm and options are limited to those within the realm of medical acceptability. Third, when there are alternatives that preserve cognition and offer a reasonable chance for cure, the degree of neurocognitive injury associated with full-dose postoperative craniospinal radiation arguably represents excessive harm and physician responsibility precludes clinicians from administering a therapy that would cause this degree of harm.

While future research will be needed to develop a systematic framework, the present analysis highlights several principles that can aid clinicians in deciding which treatment options to present to patients and their surrogates in the context of shared medical-decision making. Specifically, clinicians should consider which options best promote the patient's interests, which options minimize harm to both the patient and the decision-makers, and assure that all options represent responsible therapeutics.

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Figure.
Comparison of Estimated* Overall Survival and IQ Outcomes in Children under Age 3 treated for Medulloblastoma, XRT= Radiation Therapy, OS=Overall Survival, * Estimates are based on existing data of the treatment of children under age 3 and extrapolation from data on older children.