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Minireview

The long term effects of chemotherapy on the central nervous system

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Abstract

Cranial radiotherapy is known to have adverse effects on intelligence. A new study shows that chemotherapy is also toxic to the central nervous system, especially to neural progenitor cells and oligodendrocytes. By identifying the cell populations at risk, these results may help explain the neurological problems previously seen after chemotherapy.

Although the long-term effects of irradiation on the central nervous system (CNS) are now well-known and accepted, the long term consequences of most chemotherapeutic agents have rarely been considered, either in the development of multi-institutional cancer group studies or in the follow-up of survivors. In this issue of *Journal of Biology*, Mark Noble and colleagues [1] describe an interesting and important series of experiments that helps define the cellular basis for cognitive decline and white matter diseases (leukoencephalopathy) in patients treated with chemotherapy.

Noble and colleagues [1] have now shown that standard chemotherapeutic agents, given in dosages comparable to those used in the clinical arena, are even more toxic to CNS progenitor cells and oligodendrocytes than they are to cancer cell lines, causing both decreased cell division and cell death. The authors conducted four groups of experiments. In the first, DNA cross-linking agents - 1,3-bis(2-chlorethyl)-1-nitrosourea (BCNU) and cisplatin (CDDP) - were applied *in vitro* to purified populations of neuroepthelial stem cells, neural-restricted precursor cells, glial-restricted precursor cells, and oligodendrocyte precursor cells (O-2A/OPCs) as well as to a variety of human cancer cell lines. They found that clinically relevant concentrations of BCNU or CDDP were more toxic to lineage-committed precursor cells and neuroepithelial stem cells than to cancer cells. These effects were seen even at very low levels of exposure. Moreover, the vulnerability was not restricted to dividing cells, as non-dividing oligodendrocytes were as much at risk as the rapidly dividing neural progenitor cells.

In the second *in vitro* experiment, O-2A/OPCs exposed to sublethal concentrations of CDDP and BCNU were found to have both reduced cell division and increased differentiation into oligodendrocytes. Thus, the chemotherapy compromised the ability of the O-2A/OPCs to continue cell division and form new precursor cells.

In the third experiment, mice were treated systemically with BCNU and CDDP and then examined for evidence of cell death and cell division in the CNS. As with the *in vitro* experiments, neuronal and glial progenitor cells and oligodendrocytes were adversely affected, particularly in the subventricular zone, the corpus callosum and the dentate gyrus of the hippocampus. By examining incorporation of bromodeoxyuridine (BrdU) in adult animals, the authors found that cell proliferation in putative germinal zones was

reduced for at least 6 weeks following repeated injections of BCNU. Overall, the effects of CDDP were more transient than those produced by BCNU.

In the fourth experiment, AraC (an antimetabolite) was found to be highly toxic *in vitro* for neural progenitor cells in concentrations equivalent to those used in clinical trials. As with BCNU and CDDP, O-2A/OPCs were more sensitive to adverse effects than were the leukemia and lymphoma cell lines. In addition, sublethal concentrations of the drug were associated with suppression of cell division in clonal assays. Systemic treatment with AraC *in vivo* was also associated with cell death and reduced cell division in neuronal and oligodendrocyte precursors. Thus, despite a different mechanism of action, AraC had similar effects on the same cell populations as BCNU and CDDP.

The effect of radiation

This fascinating study is likely to act as a wake-up call for neuro-oncologists. To put the work into perspective, concerns about the long-term effects of CNS radiation were first raised in the early 1980s regarding children treated for brain tumors. Our group had reported that, of 10 children with posterior fossa tumors treated with surgery, craniospinal radiation and chemotherapy, all had evidence of either mental retardation, cognitive decline and/or learning disorders, and 40% had IQs less than 70 [2]. Others reported similar findings [3,4]. Although some children had also received chemotherapy, the overwhelming consensus was that cranial irradiation was the culprit. Two subsequent prospective studies of children irradiated for brain tumors also revealed significant cognitive decline from the baseline after only two years of follow-up [5,6].

Over the next decade, late-effects studies focused on first identifying risk factors for radiation-induced cognitive decline and then modifying treatments to reduce neurotoxicity [7]. Two of the most important of the risk factors are high dose and large volume radiation (craniospinal versus whole brain versus local) radiation. The response of investigators has been to reduce the dose and/or volume of radiation and, in some cases, to eliminate radiation entirely, adding combination chemotherapy to the treatment regimens instead. For example, attempts to reduce the dose of radiation to the brain and spinal cord from 3,600 centiGray (cGy) to 2,400 cGy led to the development of a protocol in which reduced craniospinal radiation was coupled with chemotherapy. The agents included a nitrosourea, CDDP and vincristine [8]. Of the patients treated in this way, 80% survived, suggesting that reduced CNS radiation was a viable therapeutic option if adjuvant chemotherapy was also given. Unfortunately, despite the dose reduction, a 15 to 20 point decline in IQ for most patients was identified. Although future studies are planned that further reduce the dose of craniospinal radiation to 1,800 cGy, virtually no attention has been paid to the possible contribution of the chemotherapy to the cognitive decline. Note that a nitrosourea (BCNU) and CDDP were found to be toxic to neural progenitor cells even in low doses by Noble and colleagues [1].

The greatest risk factor for radiation-induced cognitive decline is young age at the time of treatment. Cranial irradiation can be so devastating to the brains of young children (under three to five years) that, by the mid 1980s, many families opted not to treat babies and very young children who had malignant brain tumors. As a result, the US multi-institutional cancer treatment groups radically altered what had been considered 'standard' therapy (craniospinal radiation) by first delaying and then, in subsequent trials, eliminating radiation in certain 'good risk' children by using a regimen of prolonged post-operative combination chemotherapy (CDDP, cyclophosphamide, vincristine and etoposide) [9]. Current and proposed studies for infants with malignant brain tumors use even higher doses of chemotherapy, necessitating either bone marrow transplantation or peripheral stem cell support to boost the immune system, and either no craniospinal radiation or focused radiation to the tumor bed. The increased risk of neurotoxicity associated with very high doses of chemotherapy is clearly demonstrated by Noble and colleagues [1], yet these proposed studies do not take into consideration the possible effects of high-dose chemotherapy on either CNS progenitor cells or oligodendroglia in this very young, and hence vulnerable, population of patients.

Chemotherapy-induced cognitive decline in the absence of radiation

The best data on the cognitive effects of chemotherapy alone have come from studies of children with leukemia who did not have CNS leukemia. Unlike children with brain tumors - for whom there are many confounding variables that could influence intellect adversely, such as hydrocephalus, surgery, epilepsy, anticonvulsant therapy, as well as the tumor itself - children with leukemia receive chemotherapy as a preventative measure (CNS prophylaxis) and, therefore, have no specific risk factors for cognitive dysfunction. Rowland *et al.* [10] reported in 1984 that children with acute lymphoblastic leukemia (ALL) who had been irradiated for CNS prophylaxis had significantly lower IQs and worse performance on Wide Range Achievement Tests than children treated with chemotherapy alone (methotrexate injected either intrathecally (into the cerebrospinal fluid) or intravenously and intrathecally). This study and many

others confirmed the prevailing belief that chemotherapy, in the absence of radiation, did not affect intellect.

In addition, 'methotrexate leukoencephalopathy', first reported in 1978 and characterized on computed tomography (CT) scans as calcifications in the basal ganglia, cerebral atrophy and less dense areas in the white matter, was reported in children with ALL treated with cranial radiation and methotrexate [11], whereas children treated with methotrexate but no radiation did not suffer this complication. The only exception to this was those children with CNS leukemia who were unable to clear the methotrexate from the cerebrospinal fluid [12].

It was concluded from these early studies that administration of methotrexate was safe if children had no CNS disease and were not irradiated. This concept was widely accepted until 1997, when we identified a group of non-irradiated children with ALL without CNS leukemia who developed evidence of methotrexate leukoencephalopathy on CT and magnetic resonance imaging (MRI) scans associated with concomitant cognitive changes (unpublished data). A subsequent group-wide study of neuroimaging and IQ testing of children treated for leukemia confirmed these preliminary findings of methotrexate-induced leukoencephalopathy in patients that had been considered to be at low-risk [13]. Moreover, 40% of the children in that study had IQs less than 85, a striking difference from the average. As the dose and frequency of administration of methotrexate had been gradually increased over the previous two decades, the earlier optimistic predictions that methotrexate could be given with impunity were no longer valid.

Further evidence of the development of methotrexate-induced leukoencephalopathy in the absence of cranial radiation was shown in a German study of infants with medulloblastoma treated with high-dose intravenous methotrexate (5 g/m^2) and also methotrexate injected into the brain cavities (intraventricular injection), together with other chemotherapy, but no radiation [14]. Only 4 of 23 children failed to develop leukoencephalopathy. A correlation was found between the cumulative dose of intraventicular methotrexate and the grade of leukoencephalopathy, but not the number of doses of intravenous methotrexate. Although children in this study fared better cognitively than those who had been irradiated in a previous trial, the mean IQ was still significantly lower than controls. Despite these findings, as well as the accumulating data on methotrexate leukoencephalopathy in non-irradiated children with leukemia, one arm of a proposed international study for infants with medulloblastoma will include high dose intravenous methotrexate (unpublished data). Concerns over the German experience [14], however, convinced investigators to withhold intraventricular methotrexate from the trial.

It is becoming increasingly clear that not only CNS irradiation but also chemotherapy alone can cause severe neurotoxicity leading to cognitive decline and leukoencephalopathy (not to mention secondary malignancies and adverse effects on endocrine function and growth). The pediatric neuro-oncology community has recognized the adverse effects of CNS radiation and has modified treatment with the dual goals of lessening late effects while maintaining acceptable survivals. In order to accomplish this, however, chemotherapy in increasing doses has become routine. Very high dose chemotherapy, requiring bone marrow transplantation or peripheral stem cell support, is now standard therapy for children with certain brain tumors, especially for the very young. Because of the rapid myelinization that occurs in infants, the finding by Noble and colleagues [1] of the adverse effects of chemotherapy on oligodendrocytes are especially troubling. Mulhern *et al.* [15] had previously found a correlation between cognitive deficits in very young children treated with CNS radiation with or without chemotherapy and white matter loss, as identified on quantitative MRI scans. They attributed the reduction in normal-appearing white matter to radiation-induced damage to oligodendrocytes and endothelial cells [15]. It would be important to determine whether infants treated with chemotherapy alone develop a similar reduction in normal-appearing white matter, as might be anticipated based on the finding by Noble and colleagues of loss of cell division of O-2A/OPCs following chemotherapy exposure, which would presumably lead to an inability to repair damaged myelin.

There are no easy answers. We must balance the need for survival with quality of life. In the mean time, until effective targeted therapy sparing normal tissue is developed or neuroprotective therapies are available, we will need to continue using various combinations of chemotherapy and cranial radiation. The excellent correlation of the *in vitro* and *in vivo* results of Noble and colleagues' study [1] raises the hope that the technique used might allow investigators to evaluate both the effects of established agents (such as methotrexate) and newer agents on CNS neural progenitor cells and adjust treatment accordingly. As chemotherapy is almost never given as a single agent, testing these agents in combination would also be crucial. It is clear from Noble and colleagues' study [1] that chemotherapy is potentially as neurotoxic as radiation, and much closer attention needs to be paid to the long term follow-up of both children and adults who receive this form of therapy.

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