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Toxicity of Cancer Therapy in Adolescents and Young Adults (AYAs)

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Objectives: *To identify treatment-related toxicities that are either more frequent or more severe in the adolescent and young adult (AYA) oncology population. To explore differences in drug pharmacology and patient physiology that contribute to toxicities in the AYA population and to describe the impact of treatment-related toxicities on outcomes for AYA patients.*

Data Sources: *A PubMed search was undertaken using the key words Adolescent Young Adult Oncology, AYA, toxicity, bone marrow transplant, late effects, and chemotherapy. Additional toxicity information was also obtained from recent publications from cancer cooperative groups treating AYA patients.*

Conclusion: *AYA patients often experience more severe toxicities than children when treated with identical chemotherapy regimens, which can interfere with successful administration of planned treatment, as well as have profound effects on quality of life. AYA patients with cancer face the dual challenge of disease biology associated with inferior response to treatment, thus necessitating treatment intensification, while at the same time suffering higher rates of specific toxicities such as vincristine-induced neuropathy, osteonecrosis, and treatment-related mortality caused by infection.*

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IMPLICATIONS FOR NURSING PRACTICE: *AYA patients are at a higher risk for toxicities from regimens that may be tolerated by younger patients. Staff should be aware of toxicities facing this population so that appropriate supportive care measures can be utilized. Future research on the pharmacology of drugs in adolescence, hormonal effects on drug-metabolizing enzymes, cumulative exposure to different drugs in combination, and risk and severity of specific toxicities will be critical to improving the treatment of AYA patients.*

KEY WORDS: *AYA, Adolescent young adult oncology, teenage young adult oncology, toxicity*

Over the past 20 years considerable progress has been made in the treatment of pediatric malignancies, with 5-year overall survival rates as high as 80%.[1] These improvements have occurred through collaboration in cooperative group clinical trials, advances in supportive care, and the development of risk-adapted therapies. For example, treatment intensification for patients with acute leukemias with minimal residual disease following induction therapy and compressed interval therapy for the treatment of patients with Ewing sarcoma have led to significant improvements in outcomes.[2,3] Unfortunately, while considerable gains have been made in the treatment of pediatric malignancies over the past 30 years, the same progress has not occurred in adolescents and young adult (AYA) patients; the annual percent change in cancer mortality for the AYA population has lagged significantly behind younger children.[4,5] The etiology of the lack of improvement for AYA patients is multifactorial and includes differential toxicities, lack of dose intensity of adult treatment regimens compared with pediatric regimens, differences in the underlying disease biology of AYA patients, and lack of compliance. Data regarding differential toxicities experienced by AYA patients have emerged over the past 10 years but have been limited by the historically low rate of enrollment of AYA patients in clinical trials.[4-7] This review will summarize specific toxicities experienced more frequently by AYA patients compared with younger children and will explore the potential reasons underlying these differences, including pharmacology of chemotherapeutic drugs in the AYA population and the unique physiology of the AYA patient. We will highlight the importance of chemotherapy dose intensity in improving outcomes juxtaposed with the challenge of delivering adequate dose intensity in the face of increased toxicity for AYA patients. This dilemma highlights the need for focused research regarding chemotherapy drug pharmacology and toxicity in the AYA population.

PHARMACOKINETICS AND DRUG DISPOSITION

The development process for chemotherapeutic agents rarely assesses pharmacokinetics (PK) and pharmacodynamics specifically in the AYA population. Rather, PK studies are obtained in a small population of healthy volunteers and then in a population of relapsed and refractory patients, most of whom are older adults. Subsequent phase I studies in pediatric oncology populations are then undertaken, which may enroll a subset of AYA patients, but are powered to specifically evaluate PK of young children. Despite many decades of use, PK characteristics of the older, traditional cytotoxic agents among AYAs are poorly understood and these patients are often treated according to the same dosing schema used for young children as opposed to adult regimens. Dexamethasone and methotrexate, for example, represent key agents in the treatment of acute lymphoblastic leukemia (ALL); children exhibit an oral clearance rate that is twice as rapid as the rate for AYAs for both drugs.[8] Interestingly, these age-related differences correlate with a higher toxicity rate of osteonecrosis (ON) and mucositis in AYAs versus younger children with ALL.[9-15] Dose-capping strategies for vincristine and actinomycin D at 2 mg or 2.5 mg, respectively, result in lower drug exposures for AYA patients as measured by area under the curve (AUC).[15,16] For vincristine, PK studies indicate no correlation between age and drug distribution or clearance; dose capping was derived from toxicity rates in older adults and is not supported by PK evidence.[16-19] Pediatric-inspired Hodgkin lymphoma regimens have adapted vincristine PK