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Review Article

A REVIEW ON CANCER THERAPY IN DIFFERENT TYPES OF PEDIATRIC CANCERS

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ABSTRACT

Cancer refers to diseases in which abnormal cells divide uncontrollably and can invade various tissues nearby. This involves cluster of diseases involving alterations in the status and expression of multiple genes that confer a survival advantage and undiminished proliferative potential to somatic or germinal cells. Cancer cells display a broad spectrum of genetic alterations leading to disturbances in molecular pathways regulating cell growth, survival, and metastasis. When such changes manifest in majority of patients with a specific type of tumour, these can be used as biomarkers for detection and developing targeted therapies, besides predicting responses to various treatments. In terms of behavior, tumours are either 'benign' or 'malignant'. Leukemia is most common type of cancer among the pediatric population. Cancer chemotherapy is based on tumor cell growth and how drugs affect this growth. All chemotherapy orders are written by pediatric oncologists and countersigned, usually by another physician. With recurrent disease, various salvage protocols may be used; with refractory disease, a limited number of phase I/II studies are available through the Children's Oncology Group (COG).

KEYWORDS: *Cancer, Types of cancer, Chemotherapy*

INTRODUCTION

Cancer is a term that refers to diseases in which abnormal cells divide uncontrollably and can invade various tissues nearby. Neoplastic cells can also spread to other parts of the body through blood and the lymphatic system. [1] Cancer in children and adolescents is rare and biologically very different from cancer in adults. It is estimated that about 148000 cancers occurred during 2008 in children aged 0–14 years in less-developed regions. In India cancer is the ninth common cause for the deaths among children between 5 to 14 years of age.

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The proportion of childhood cancers relative to all cancers reported by Indian cancer registries varied from 0.8% to 5.8% in boys, and from 0.5% to 3.4% in girls. [2]

CANCER

Cancer is a cluster of diseases involving alterations in the status and expression of multiple genes that confer a survival advantage and undiminished proliferative potential to somatic or germinal cells. Alterations primarily in three main classes of genes viz., (proto) oncogenes, tumour suppressor genes and DNA repair genes collectively contribute to the development of cancer genotype and phenotype

that resists the natural and inherent death mechanism(s) embedded in cells (apoptosis and like processes), coupled with disregulation of cell proliferation events. [3]

Cancer biomarkers:

Every cell type has a unique molecular signature, referred to as biomarkers, which are identifiable characteristics such as levels or activities of a myriad of genes, proteins or other molecular features. Biomarkers are therefore, an objective measure or evaluation of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. This includes all diagnostic tests, imaging technologies, and any other objective measures of a person's health status. Biomarkers are subject to dynamic modulation, and are expected to enhance our understanding of drug metabolism, drug action, efficacy, and safety. These can also facilitate molecular definition of diseases, provide information about the course of disease and predict response to therapies. Cancer cells display a broad spectrum of genetic alterations that include gene rearrangements, point mutations, and gene amplifications, leading to disturbances in molecular pathways regulating cell growth, survival, and metastasis. When such changes manifest in majority of patients with a specific type of tumour, these can be used as biomarkers for detection and developing targeted therapies, besides predicting responses to various treatments. [3]

Clinical assessment

The management of a patient with cancer is dependent upon a number of pieces of information that can be gathered about the tumour:

- The tissue of origin
- Benign or malignant
- Tumour grade
- Tumour stage

Benign tumours can normally be removed by surgery. Malignant solid tumours will, if possible, be surgically resected, probably followed and even preceded by other treatment modalities. More diffuse tumours such as leukaemias with circulating tumour cells require systemic chemotherapy. A histopathologist will 'grade' the tumour in terms of its state of differentiation on a scale from well, through moderately to poorly differentiated. For example, normal colonic epithelial cells from simple tubular glands; cancerous colonic cells largely organized into glandular structures, albeit in a disorderly fashion, would be graded as well differentiated (low grade). At the other end of the spectrum, poorly differentiated (high grade) tumours show little if any resemblance to the tissue of origin. Poorly differentiated tumours tend to be more aggressive, growing faster and more likely to have metastasized before the patient has presented. Thus, patients with poorly differentiated tumours tend to have a worse prognosis and might be selected for more aggressive treatment. [4]

Tumour 'staging' is a semi quantitative assessment of the clinical gravity of the disease. A complete profile can be built up from knowing the size of the primary tumour, the extent of local lymph node involvement and the presence or absence of distant metastasis. In this tumour node metastasis (TNM) staging, the larger the primary tumour and the more local nodes involved then the more advanced the stage with a concomitantly poorer prognosis. Significantly, the presence of metastatic disease immediately assigns the patient to the most advanced stage, irrespective of the size of the primary tumour, highlighting the importance of early detection and intervention to patient survival. [5]

Classification of tumors:

In terms of behavior, tumours are either 'benign' or 'malignant'. **Benign tumours** are generally slow-growing expansive masses that compress rather than invade surrounding tissue. As such they generally pose little threat, except when growing in a confined space like the skull, and can usually be readily excised. However, many so-called benign tumours have malignant potential, notably those occurring in the large intestine, and these should be removed before malignancy develops. [6]

Malignant tumours are usually rapidly growing, invading surrounding tissue and, most significantly, colonizing distant organs. The ability of tumour cells to detach from the original mass (the primary tumour) and set up a metastasis (secondary tumour) discontinuous with the primary is unequivocal proof of malignancy. Tumours are also classified according to their tissue of origin; recognition of the parent tissue in a lymph node metastasis could establish the location of a hitherto undiagnosed primary tumour. [7]

Current status of cancer in India

The types of cancers that develop in children and adolescents differ from those that develop in adults. The predominant types of pediatric cancers are leukemia (26%), cancers of the brain and central nervous system (CNS) (18%), and lymphoma (14%). Some of the cancers that develop in children are rarely seen in older individuals, notably those cancers that arise from embryonic cells and originate in developing tissues and organ systems. Embryonal cancers include Neuroblastoma (sympathetic peripheral nervous system), Wilms tumor or nephroblastoma (developing kidney), Medulloblastoma (brain), rhabdomyosarcomas (muscle), and retinoblastoma (retina of the eye). Some pediatric cancers, particularly those that are more common in adolescents, are more similar to those that arise in adults (e.g., acute myeloid leukemia, Hodgkin lymphoma, thyroid cancer, and melanoma). [8]

Pediatric cancers represent 1% of all new cancers diagnosed in the country. Because these cancers occur in the context of rapid growth and development, most experts strongly recommend that they be treated at medical centers specialized in childhood cancer by multidisciplinary teams including pediatric oncologists, surgeons, radiation oncologists, and other specialists. At pediatric cancer centers, treatment protocols are available for most types of cancer that occur in children and adolescents, and the opportunity to participate in clinical trials is offered to most patients and their families. Clinical trials are generally designed to compare a potential improvement in therapy with therapy that is currently accepted as standard; improvements may result in an increase in cure rates or a reduction in acute or long-term complications. Member institutions of the Children's Oncology Group (COG), a National Cancer Institute-supported clinical tri-als group, care for more than 90% of US children and adolescents diagnosed with cancer. The (childrensoncologygroup.org) COG has nearly 100 active clinical trials open at any given time, which include studies to test the efficacy of new treatments for many types of childhood cancers at diagnosis or recurrent diseases, improve understanding of the underlying biology of these diseases, and improve supportive care and survivorship. Children and adolescents diagnosed with types of cancer more commonly seen in adults also benefit from treatment in pediatric cancer centers. [8]

TYPES OF CHILDHOOD CANCER:

Childhood cancer is a general term used to describe a range of cancer types and noncancerous tumors found in children. Childhood neoplasia may also be called pediatric neoplasia. According to cancer facts and figures 2014 some are the most common types of neoplasia in children under 14 years old are:

LEUKEMIA (accounts for about 31% of childhood neoplasia cases) Leukemia is a kind of cancer that starts in blood-forming tissues such as bone marrow and causes large numbers of abnormal blood cells which will enter the blood stream.

Acute lymphoblastic leukemia (ALL)

Acute lymphoblastic leukemia (ALL) reflects a heterogeneous group of diseases that are characterized by variability in immunophenotype, cytogenetics and clinical features. ALL is the most common pediatric malignancy. [9]

Acute myeloid leukemia (AML)

Acute myeloid leukemia (AML) is cancer that starts inside bone marrow. This is the soft

tissue in the center of bones that helps form all blood cells. The cancer grows from cells that would normally turn into white blood cells.

Persons with this type of cancer have an abundance of abnormal immature cells inside their bone marrow. The cells grow very quickly, and replace healthy blood cells. The bone marrow, which helps the body fight infections and makes other blood components, eventually stops working correctly. Persons with AML are more likely to have infections and have an increased risk of bleeding as the numbers of healthy blood cells decrease.

The following things can lead to some types of leukemia, including AML:

- Blood disorders, including polycythemia vera, thrombocythemia, and myelodysplasia
- Certain chemotherapy drugs, including Etoposide and drugs known as alkylating agents.
- Certain chemicals (for example, benzene). [10]

BRAIN AND CNS tumors (21%), including tumors of the spinal cord)

Astrocytoma

Low-grade astrocytomas may develop in any region of the central nervous system (ONS) but most commonly develop supratentorlally in the cerebrum of both children and adults. The brain stem is the next most common site, while these tumours are distinctly uncommon in the cerebellum. Within the cerebrum, they arise roughly In proportion to the relative mass of the different lobes; hence, the frontal lobe is the commonest location, followed by the temporal lobe. [11]

Brain stem glioma

Brainstem gliomas are a heterogeneous group of tumors occurring in the brainstem and cervicomedullary junction. [12], [13]

Craniopharyngioma

Craniopharyngioma is a non-glial intracranial tussmor derived from a malformation of Embryonal tissue. [14]

Desmoplastic infantile ganglioglioma

Ependymoma

Any tumor that arises from the glial cells in the brain is called a “glioma.” Glial cells provide support and protection for the nerve cells, or neurons, in the brain. One type of glioma is the ependymoma. Ependymomas arise from ependymal cells that line the ventricles of the brain and the center of the spinal cord. Occasionally, ependymal cells are found within the brain itself. Ependymomas are soft, grayish or red tumors which may contain cysts or mineral calcifications.

- **High-grade glioma**
- **Medulloblastoma**

Medulloblastoma is a malignant and invasive Embryonal tumor of the cerebellum, corresponding histologically to World Health Organization (WHO) grade IV, that has sometimes been referred to as an infratentorial primitive neuroectodermal tumor, or PNET. [15]

Atypical teratoid rhabdoid tumor

Neuroblastoma (7%), a tumor of immature nerve cells that often starts in the adrenal glands, which are located on top of the kidneys and are part of the body’s endocrine (hormonal) system.

Wilms tumor (5%), a type of kidney tumor.

Non-Hodgkin lymphoma (6%) and **Hodgkin lymphoma** (4%), cancers that begin in the lymph system.

Rhabdomyosarcoma (3%), a type of tumor that begins in the striated muscles, which is part of the skeletal voluntary muscles that people can control. Other, rare soft tissue sarcomas also occur. **Retinoblastoma** (3%), an eye tumor. **Osteosarcoma** (3%) and **Ewing sarcoma** (1%), tumors that usually begin in the bone. **Germ cell tumors,** rare tumors that begin in the testicles in boys or ovaries in girls. Even more rarely, this tumor can begin in other places in the body, including the brain.

Pleuropulmonary blastoma, a rare kind of lung cancer. **Hepatoblastoma** and **hepatocellular carcinoma** types of liver tumors.[8], [16]

DIFFERENT TYPES OF THERAPIES USED FOR THE TREATMENT OF CANCER

Cancer treatment is usually a combination of a number of different modalities. If the tumour is amenable to surgery, then surgery is the single most effective tool in the anticancer armamentarium. Targeted radiotherapy is another option, as are combinations of anticancer drugs. Most conventional anticancer drugs have been designed with deoxyribonucleic acid (DNA) synthesis as their target. Therein lies the problem, in that tumour cells are not the only proliferating cells in the body; cells that line the alimentary tract, bone marrow cells that generate red blood cells and cells to fight infection, and epidermal cells including those that generate hair are all highly proliferative. Thus, patients with cancer receiving chemotherapy commonly suffer unwanted (hair loss) and sometimes potentially life-threatening (anaemia and proneness to infections) side effects that limit treatment.

The new generation of drugs has targets removed from the direct synthesis of DNA; they affect the signals that promote or regulate the cell cycle, growth factors and their receptors, signal transduction pathways and pathways affecting DNA repair and apoptosis. Each of these pathways may be affected by activating mutations that predispose to cancer and, thus, offer the potential as a target for inhibition. Other strategies focus on either attempting to target tumour cells specifically by conjugating cell toxins to tumour-specific antibodies (magic bullets), or slowing down cancer progression by affecting cell adhesion, proteolytic enzyme activity and angiogenesis. [4 -7]

DRUGS USED FOR THE CHEMOTHERAPY OF CANCER

Cancer chemotherapy is based on an understanding of tumor cell growth and how drugs affect this growth. After cells divide, they enter a period of growth (ie, phase G1), followed by DNA synthesis (ie, phase S). The next phase is a premitotic phase (ie, G2), which is followed by a mitotic cell division (ie, phase M).

Cell division rate varies for different tumors. Most common cancers increase very slowly in size compared with normal tissues, and the rate may decrease further in large tumors. This difference allows normal cells to recover more quickly from chemotherapy than malignant cells; it is the rationale behind current cyclic dosage schedules. Antineoplastic agents interfere with cell reproduction. Some agents are cell cycle specific, whereas others (eg, alkylating agents, Anthracycline, cisplatin) are not phase specific. Cellular apoptosis (ie, programmed cell death) is also a potential mechanism of many antineoplastic agents.

All chemotherapy orders are written by pediatric oncologists and countersigned, usually by another physician. With recurrent disease, various salvage protocols may be used; with refractory disease, a limited number of phase I/II studies are available through the Children's Oncology Group (COG). [17]

Pediatric Acute Lymphoblastic Leukemia Medication

Drugs commonly used during remission induction therapy include dexamethasone or prednisone, vincristine, asparaginase, and daunorubicin. Consolidation therapy often includes methotrexate (MTX) and 6-mercaptopurine (6-MP) or cyclophosphamide and cytarabine. Drugs used for intensification include cytarabine, cyclophosphamide, etoposide, dexamethasone, asparaginase, doxorubicin, MTX, 6-MP, and vincristine. Continuation therapy is based on oral 6-MP and MTX with pulses of vincristine and glucocorticoid (prednisone or dexamethasone). Intrathecal chemotherapy includes primarily MTX, which may also be combined with hydrocortisone and cytarabine (“triple-intrathecal therapy”). Imatinib is also approved for children newly diagnosed with Ph+ ALL. [18]

It is important to note that corticosteroids can adversely suppress the function of the hypothalamic pituitary adrenal axis and such suppression can have adverse effects on a patient's ability to respond to different stresses, such as severe infection. A Cochrane Database review of 7 studies showed adrenal insufficiency occurred in nearly all ALL patients in the first days after cessation of glucocorticoid therapy. Although the majority of patients recovered within a few weeks, a small number of patients had adrenal insufficiency lasting up to 34 weeks. [19]

Pediatric Neuroblastoma Medication

Antineoplastic drugs have a narrow therapeutic index and effective doses usually cause severe toxicities, some of which can be life threatening. These agents are almost invariably given in combination. Commonly used combinations include the following:

- Vincristine, cyclophosphamide, and doxorubicin
- Carboplatin and etoposide
- Cisplatin and etoposide
- Ifosfamide and etoposide
- Cyclophosphamide and topotecan

Consolidation regimens

- Carboplatin and etoposide with melphalan or cyclophosphamide.
- Thiotepa and cyclophosphamide.
- Melphalan and total body irradiation [20], [21]

Pediatric Osteosarcoma Medication

The chemotherapeutic drugs most active in osteosarcoma are doxorubicin, cisplatin, and high-dose methotrexate (for which a low dose is ineffective). Whether chemotherapy dose escalation can improve outcome in patients with a poor histologic response is the subject of an ongoing study in the United States and Europe. One report suggests that, although dose intensification increases the number of patients with a good histologic response, it does not change overall survival. [22]

In addition, other therapies are being tested, such as the following:

- Anthracycline escalation using a cardioprotectant
- Muramyl tripeptide phosphatidyl ethanolamine (MTP-PE) and other immune enhancers (eg interferon).
- Monoclonal antibody against the Her2/neu antigen, which is over expressed in some
- osteosarcomas.[23], [24]

As usual, physicians caring for patients with osteosarcoma should consult a pediatric oncologist affiliated with a center that participates in national or international trials to determine both the current standard treatment protocol and whether an appropriate investigational study is open for patient accrual. [25]

Wilms Tumor Medication

As previously stated, several cytotoxic agents may cause liver damage in patients treated for Wilms tumor. Reports have documented hepatic toxicity with the combination of vincristine and dactinomycin even in the absence of radiation therapy (which many early reports suggested was the major etiologic factor in liver damage). [26]

The fact that patients who received less dactinomycin than others (ie, those with relatively low-stage disease) had a low incidence of 2.8% suggests a dose-related toxicity for dactinomycin. [27]

Patients who survive Wilms tumor are at risk because inherited disposition and treatment (eg, chemotherapy, irradiation) can induce second malignant neoplasms. Although most secondary malignant neoplasms reported (eg, bone tumors, breast and thyroid cancers) have occurred in irradiated areas, certain chemotherapeutic agents, including doxorubicin, dactinomycin, and vincristine, may contribute to an increased risk for secondary malignancies. [28]

Pediatric Medulloblastoma Medication

Chemotherapeutic agents are continually evolving. Historically, the most active drugs have been DNA alkylators. These agents cause DNA damage and disrupt DNA replication. The agents with the longest clinical history in the treatment of medulloblastoma are vincristine, lomustine (CCNU), and cisplatin. [29]

Pharmacological Pain Management Modalities

Prescription of analgesics should follow the World Health Organization's analgesic ladder, which recommends non-opioids for mild pain and opioids for moderate to severe pain. Combining opioid and non-opioid therapies may improve analgesia, as may the addition of adjuvant agents. Chemotherapeutic agents and radiotherapy may produce potent analgesia in pediatric cancer pain by reducing tumor load.

Analgesia should be given to children by the simplest, most effective, and least painful route. Oral analgesia is usually the first choice. Intravenous (i.v.) administration has its advantages (e.g., rapid onset, bioavailability, and easier titration), particularly in pediatric patients who have long-term i.v. access. Patient-controlled analgesia (PCA) may be used in appropriate children over 6–7 years old. Using this technology, children self-administer intermittent opioid boluses, catering for individual variation in pain and drug pharmacology, and allowing patients to balance their own analgesia and side effects. Subcutaneous administration is an alternative if i.v. access is not feasible. Intramuscular analgesia is painful, and rectal administration is discouraged due to infection risk in cancer patients.

Unless pain is truly unpredictable, opioids should be given regularly, with "as needed" doses prescribed to treat breakthrough pain. [30]

Non-Opioid Analgesics

Acetaminophen (paracetamol) is the most commonly used non-opioid analgesic, and i.v. administration (where available) is effective in similar doses, when oral administration is not possible. Nonsteroidal anti-inflammatory drugs impair platelet function and are often contraindicated in pediatric oncology patients who are at risk of thrombocytopenia and bleeding.

Opioid Analgesics

- Oral codeine may be used for moderate cancer pain, but it has limitations due to variable conversion to morphine, its active metabolite.
- Morphine is one of the most commonly used opioids for moderate to severe pediatric cancer pain and is generally the first-line opioid agent. Sustained-release oral morphine preparations are available.
- Oxycodone is commonly used to treat moderate to severe cancer pain; it has a relatively high oral bioavailability.
- Hydromorphone and fentanyl are alternative opioids to morphine when dose-limiting side effects arise. Fentanyl has a rapid onset due to its high lipid solubility and shorter half-life.
- Methadone has a long and highly variable half life, so there is a risk of accumulation and delayed sedation and toxicity with its use.
- Opioid switching often changes the balance between analgesia and side effects. It is useful in managing dose limiting side effects or tolerance to opioids, which is a less common problem in pediatric cancer pain. All opioids can potentially cause the same range of side effects. Although tolerance develops to most side effects, e.g., sedation, nausea, and pruritis, as with adults, children do not develop tolerance to
- constipation, so regular laxatives should be given.

Adjuvant Agents

Adjuvant analgesics may be added to improve analgesia or allow dose reduction of opioids to minimize side effects. Classes of adjuvant drugs include antidepressants, anticonvulsants, local anesthetics, and corticosteroids.

Anesthetic approaches to cancer pain, e.g., nerve blocks, are usually confined to children with regional pain unresponsive to other analgesics. [31]

CONCLUSION

Childhood cancer, though relatively rare compared with cancer in older adults, is generally more responsive to therapy and has contributed immensely to an understanding of the pathogenesis of neoplasia. classification by histology and new molecular laboratory techniques are proving key elements for improvements in etiology, prevention, screening for early detection, recognition of high risk groups, diagnosis, treatment, and prognosis.

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