Understanding Dose Intensity is Essential for Optimizing Chemotherapeutic Regimens

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Recent advances in the treatment of antineoplastic disorders have placed clinical cures within reach. As information has accumulated on antineoplastic pharmacology, immunology, tumor biology, cytokinetics, and drug resistance, therapeutic strategies have been developed to maximize tumor cell kill and to overcome or minimize resistance, enhancing the potential for cure by chemotherapy. An important component of many emerging strategies is dose intensity, a concept that stresses that the amount of drug delivered per unit time is a major determinant of outcome. Dose intensity acknowledges 1) the clonal nature of tumor growth and thus the need to eradicate every viable tumor stem cell, 2) the heterogeneity within tumors of cell sensitivity to chemotherapy, and 3) the existence of essential dose-response relationships in chemotherapeutics.

Three major advances are moving dose intensity into the clinical arena: specialized dosage forms for more targeted drug delivery, synthetic chemotherapy analogues that have greater safety and activity against resistant clones, and clinical improvements in supportive care. It now seems likely that the concept of dose intensity will emerge as an important new paradigm for optimizing chemotherapeutic regimens.

The therapeutic implications of dose intensity are significant for practicing oncologists, oncology pharmacists, and other health-care personnel who administer chemotherapy. Oncologists who understand the potential applications of dose intensity, as well as its limitations, will be able to integrate the concept into individual patient treatment programs.

An important component of many emerging strategies is dose intensity.

Dose Intensity
Dose intensity is the amount of drug delivered per unit time, expressed as mg/m²/week (regardless of schedule). Emphasis is placed on the time over which chemotherapy is administered.

Ardent supporters of the dose intensity concept believe that the most important adverse effect of treatment may be death from insufficient treatment or from a lack of dose

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intensity. Certainly, one of the most common problems with chemotherapy is toxicity; however, concern over toxicity may at times be out of proportion to the fatal consequences of the disease itself. For example, after the original National Cancer Institute MOPP (mechlorethamine, Oncovin (vincristine), procarbazine, prednisone) protocol for Hodgkin’s disease was modified to reduce treatment-induced toxicity, dose intensity decreased 29-38%. However, overall disease-free survival also decreased by 33-35%. Translated to a national forecast, the decreased dose intensity could result in the overall loss of lives of 1000 patients per year, a “side effect” that far exceeds the treatment-induced mortality from full doses of MOPP chemotherapy.

Skeptics of dose intensity emphasize that the concept neglects important host variables such as drug disposition, tumor burden, and tumor stage. Moreover, the lack of a demonstrable dose-response curve for some drugs calls into question the necessity of dose intensity in certain situations. Clearly much research remains to be done; nevertheless, dose intensity is finding a niche in the clinic, especially in the treatment of lymphomas, breast cancer, ovarian cancer, small cell lung cancer, and advanced colorectal cancer. In these diseases, better response rates have been correlated retrospectively with increased dose intensity.

Clinical trials have demonstrated important correlations between dose intensity and response rates for cisplatin in ovarian cancer, doxorubicin and cisplatin in endometrial cancer, 5-fluorouracil (5-FU) in advanced colorectal cancer, and multiagent combinations for Hodgkin’s disease, breast cancer, and small cell lung cancer. Ongoing clinical trials designed to validate these findings prospectively and to evaluate the importance of dose intensity in other conventional chemotherapeutic regimens should further delineate the diagnoses and treatment regimens for which dose intensity is essential to therapeutic outcome. Moreover, as the concept is incorporated into the design and reporting of clinical trials, interstudy comparisons of data and results may be improved.

Supportive Care Techniques Reduce Toxicity
Designing safe regimens that maximize dose intensity should be facilitated by the recent strides in supportive care. Techniques that reduce the risks of chemotherapy-induced toxicity are critical to the effective management of many cancers. Supportive measures such as protected environments, broad-spectrum antibiotics, analgesics, and blood products have decreased the risks associated with high-dose chemotherapy and enabled patients to tolerate more dose-intensive therapies. The new drugs and biological products available to reduce the morbidity associated with chemotherapy-induced myelosuppression include potent antibiotics (such as ceftriaxone, ciprofloxacin, and imipenem), blood products, intravenous immunoglobulins, and hematopoietic growth factors. The hematopoietic growth factors are undergoing rigorous clinical evaluation in myelosuppressed patients, since they stimulate the production of macrophages, granulocytes, or both. The hope is that these compounds may eventually eliminate myelosuppression as a dose-limiting side effect of chemotherapy.

Improved antiemetic combinations also favor the use of higher doses in individual patient regimens. Serotonin antagonists, now under investigation, will soon be added to the armamentarium of effective antiemetics for chemotherapy. Effective antiemetic therapy for regimens containing anthracycline, cisplatin, or dacarbazine are necessary so that patients can tolerate full therapeutic doses of these agents.

Synthetic Analogues Offer Greater Potential Safety and Efficacy.
Advances in drug development have made possible the synthesis of analogues of some of the more active chemotherapeutic agents. These agents offer potential advantages over the parent compounds in terms of safety and efficacy against resistant cell lines. Two such compounds are carboplatin and mitoxantrone. These drugs, which have become commercially available in recent months, are synthetic analogues of cisplatin and doxorubicin, respectively. The enhanced antitumor activity of these and other analogues
in clinical trials, coupled with improved safety profiles that allow increased dose intensity, might translate into greater disease-free survival for certain patient populations.

**Specialized Dosage Forms Enhance Antitumor Activity**

Recent technologic developments have made possible sophisticated drug delivery devices, genetically engineered compounds, liposomal drug-carrier systems, and monoclonal antibodies (MoAbs) to enhance targeted drug delivery, thereby improving the therapeutic index of drug treatments. These new formulations currently are being investigated as tools to increase achievable dose intensity while minimizing systemic toxicity.

*Decreased dose intensity could result in the overall loss of lives of 1000 patients per year.*

Regional drug delivery by intraarterial administration of chemotherapy improves the therapeutic index by providing high drug concentrations to cancerous tissue while minimizing the systemic drug delivery. Advanced by improvements in vascular access devices and in implantable or programmable infusion pumps, the technique offers another means of maintaining dose intensity. Results with fluorouracil (FUDR) administered intrahepatically via an implantable infusion pump to patients with metastatic liver disease have been favorable. Future applications are promising.

Other targeted drug delivery options are being investigated to maximize dose intensity at the tumor site. Chemomobilization uses drug-loaded microspheres to create a “chemotherapy bullet” capable of delivering high concentrations of drug to highly vascular tumors. Liposomes are phospholipid vesicles with aqueous compartments that entrap drugs and serve as drug carriers. Liposomal carriers are being evaluated for doxorubicin, methotrexate, and melphalan.

New approaches to treatment are being investigated based on dose intensity principles. “Front-end-loading” regimens call for dose-intense drug therapies in early stages of disease to debulk effectively the tumors and inhibit the emergence of resistance. “Leap frog” sequencing regimens capitalize on the benefits of dose intensity. Higher doses are better able to reduce bulk disease and suppress resistant clones. The most active drugs against the tumor are initially given at high dose intensity to reduce the bulk of the sensitive tumor mass. During this phase in the sequence, drugs most active against the likely resistant clones are given at a lower dose intensity to hold resistant clones in check. After debulking the tumor, the agents active in bulk disease may be deleted or decreased so that dose intensity may be increased for the drugs most active against the resistant mutants. Chemotherapy administered in such a sequencing fashion may improve overall cell kill and potential for cure.

*Genetically engineered compounds enhance targeted drug delivery.*

Biochemical modulation using combinations of drugs enhances overall antitumor activity. Folinic acid combined with 5-FU enhances 5-FU’s activity by providing an excess of intracellular reduced folates, which increases the inhibition of thymidylate synthetase. This modulatory action increases the cytotoxic potential of 5-FU in advanced colorectal cancer.

Treatment programs that optimize dose intensity are finding their way to the oncology clinic. The use of supportive therapies such as parenteral antibiotics, nutritional support, blood products, and hematopoietic growth factors are becoming standard components of oncology practice in both inpatient and outpatient settings. The challenge for oncologists facing patient care decisions will be to balance risk and benefit in a reasonably cost-efficient manner.

Physicians who desire additional information may write Stephen L. Huber, M.S., or Nicky Dozier, Pharm.D., Division of Pharmacy, Box 90, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-2870.
The multiple endocrine neoplasia (MEN) syndrome has become one of the most interesting subjects in medicine and surgery over the last two decades. MEN consists of various subtypes whose treatment requires various strategies and the combined efforts of members from practically all disciplines of medicine.

MEN I is a highly penetrant autosomal-dominant disease involving the pituitary gland, parathyroid gland, and pancreas. MEN II—a carcinoma of the medullary thyroid—is also genetically based and may appear with or without parathyroid adenoma or hyperplasia and bilateral pheochromocytoma. Such cases are termed MEN IIA. MEN IIB is identical to IIA, except that mucosal neuromata—possibly involving the gastrointestinal tract from the mouth to the anal opening—are also present. MEN IIB may also be associated with musculoskeletal deformities or marfanoid habitus. MEN IIB has also been termed MEN III.

Autotransplantation is Ideal for MEN I Parathyroid Hyperplasia

Most patients with MEN I are referred to us for management of hypercalcemia, which often suggests parathyroid hyperactivity or the presence of a pancreatic tumor, with symptoms suggesting the presence of a functioning islet cell tumor. This kind of tumor may produce insulin, resulting in hypoglycemia; glucagon, resulting in diabetes with or without skin ulcerations; gastrin, resulting in gastric ulcers; or vasoactive intestinal peptide, causing severe diarrhea and hypokalemia. Patients may also be referred because of amenorrhea with or without galactorrhea. Although the presenting symptoms are usually related to only one tumor, careful examination usually reveals pituitary or parathyroid tumors, as well as pancreatic tumor.

In our studies at the M. D. Anderson Cancer Center, we have studied five families with MEN I syndrome. In one of these families alone, 9 of 245 members identified so far had the disease. In this syndrome, 95% of patients have hypercalcemia that is due to hyperplasia of the parathyroid glands. Steve Marks, M.D., and Gerald Orebach, M.D., of the National Institutes of Health have found some experimental evidence that this hyperplasia is most likely due to parathyroid-stimulating hormone, but the origin of this factor has yet to be established. We found that the ideal approach for treating this particular condition is to remove the four parathyroid glands and transplant half of one gland in the forearm to allow monitoring of serum parathyroid hormone and calcium levels. It is also possible to remove three and a half parathyroid glands, leaving half a gland in the neck, marked by a silver clip to aid in x-ray localization. If hypercalcemia recurs, the parathyroid tissue can be removed and transplanted in the forearm. This form of autotransplantation was developed by Robert C. Hickey, M.D., at M. D. Anderson and by Sam Wells, M.D., at Duke University in independent and simultaneous studies.

Pancreatic tumors may secrete several hormones, but one is usually predominant and causes the clinical symptoms.

MEN I Pancreatic Tumors Were Found to be Multiple

We have identified and examined 20 patients from the five families with MEN I syndrome. Fourteen had hormone-producing pancreatic tumor, such as gastrinoma, insulinoma, glucagonoma, vipoma, or polypeptide-producing tumor. Multiple pancreatic tumors usually occurred throughout the pancreas. We found that the pancreatic tumor may secrete several hormones, but one was usually predominant and caused the clinical symptoms. The treatment of choice generally was total pancreatectomy, especially in patients with gastrinoma, since the tumor is found in diffuse forms throughout the pancreas. Subtotal pancreatectomy in patients with insulinoma has been successful, with no recurrence up to 12 years. Long-term follow-up is needed to determine the ideal approach.

Pancreatic tumors have the potential of metastasizing to the liver, in which case the treatment of choice is liver embolization. Chemotherapy in the form of 5-fluorouracil, streptozotocin, and doxorubicin has been shown to be effective in 20 to 30% of patients. Also effective is a somatostatin analogue, SMS 201-995 (Sandoz Drug Co.), which palliates the symptoms caused by an excess of the
gastrointestinal peptide; however, this drug may not inhibit tumor growth. Interferon is currently being investigated.

Anterior pituitary tumors were seen in 40% of patients with MEN I syndrome. Of these, 85% were prolactin-producing tumors, and 15% were growth hormone-producing tumors (acromegaly). Women had amenorrhea, which was sometimes accompanied by galactorrhea and infertility, whereas men were impotent and sterile. We found that the best treatment for prolactinoma was the administration of the dopamine agonist bromocriptine. With this drug, tumor size decreases, the serum prolactin level returns to normal, and the pituitary gland may reach normal size. Women will regain their menses and fertility, and men will regain their potency and fertility. Bromocriptine, taken by mouth, may initially cause slight nausea, headache, and blurred vision, but these symptoms usually disappear with continued treatment. Recently, an experimental drug called CV 205-502 (Sandoz) has been used in a limited number of centers. This drug is also a dopamine agonist but, unlike bromocriptine, is not an ergot alkaloid derivative. We administered CV 205-502 to 15 patients with prolactinoma. In all patients serum levels returned to normal and tumor size decreased. No patient complained of the side effects we have seen with bromocriptine.

In patients with acromegaly, we found that transsphenoidal surgery is the best treatment. SMS 201-995, an octreotide acetate, was recently found to be successful in the treatment of this disorder, but its long-term effectiveness remains to be proved.

Generally, family members of MEN patients should be screened routinely. We currently know that the MEN syndrome gene maps to chromosome 11, though its exact location remains to be identified. This may shed more light on the genetic aspects of this disease and possibly result in genetically based screening techniques. Until genetic techniques become available, clinical screening should be performed for all family members of patients diagnosed with MEN I. In addition to a careful history and physical examination, a number of routine assays should be performed: serum calcium and phosphorous levels, basal levels of pancreatic hormones, basal serum prolactin level, growth hormone level, and adrenocortical-stimulating hormone level.

Calcitonin Measurements Detect MEN II

MEN II, or medullary thyroid carcinoma, is a tumor of the C-cells (parafollicular cells), which secrete calcitonin. MEN II may occur in the sporadic or familial form. Like MEN I, the familial form of MEN II is a highly penetrant autosomal-dominant trait. The patient's prognosis is best when disease is localized in the thyroid gland. The disease should be treated by total thyroidectomy, and the lymph nodes in the neck should be sampled. If they are involved, a modified bilateral neck dissection should be performed. If there is muscle involvement, a radical neck dissection with removal of these muscles should be done. Radiotherapy in these cases may be considered, especially if the surgeon has a high degree of suspicion of residual disease. However, medullary carcinoma is resistant to radiotherapy, and iodine-131 therapy has not proved effective; in fact, no effective chemotherapy has yet been established for distant metastases.

Over the last 20 years, M. D. Anderson has treated 225 patients with MEN II, which constitutes the largest number of patients diagnosed at one institution. Measurement of calcitonin at basal or after pentagastrin stimulation is the best method of detecting MEN II. We were among those who established the radioimmunoassay of calcitonin. We also showed that serum calcitonin is high in the normal fetus and the normal pregnant mother. The high calcitonin in the fetus appears to be important in fetal bone formation. In pregnant mothers, it appears to prevent bone loss during pregnancy by inhibiting bone resorption induced by the high parathyroid hormone present during pregnancy. We also found that serum calcitonin, which is high during early life, progressively decreases with age and reaches the normal adult level between ages 7 and 10 years. In children of family members with MEN II, however, we found that the serum calcitonin level increases with age. Recently, we diagnosed MEN II in a 3-month-old child. 

Family members of MEN patients should be screened routinely.
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of black may be present, which may indicate malignant transformation. The borders, unlike those of common nevi, are ill defined and tend to merge into the surrounding skin. About 90% of dysplastic nevi occur in the trunk, but they also can appear in sun-protected areas such as the female breast, the scalp, or the buttocks. The latter three areas are diagnostically important, since common acquired nevi are less common in these locations. For the most part, dysplastic nevi proper appear only after puberty, though rudimentary nevi have been identified in individuals as young as 5 years old. If the syndrome has not developed by age 25, it likely will not do so.

"Our screening process is quite simple," Duvic said. "We perform a complete examination of the skin, scalp, and the mouth. It is also important to examine the eyes, since ocular nevi and melanoma are a possibility. We pay attention to any moles in which the dimensions, pigment, or border has changed. Symptoms like bleeding or burning could be a sign that the mole is in the process of transformation. When a patient is initially diagnosed with dysplastic nevus syndrome, we generally encourage other family members to be examined because of the genetic basis of this disorder. There is usually someone else in the family who has had melanoma, which may help confirm the diagnosis."

Dysplastic nevi are particularly important because of the associated risk of melanoma.

"That's why it's essential for an experienced dermatopathologist to confirm any clinical diagnosis," Duvic said. "Sometimes lesions that appear dysplastic are malignant melanomas upon pathological examination. To some degree, differentiating dysplastic nevi from malignant melanoma is subjective and depends on the experience of the pathologist."

Dysplastic nevus syndrome, also known as atypical mole syndrome, was originally described in two families with familial melanoma. This syndrome can also be sporadic. Individuals with the sporadic condition, type A, have no family history of either the syndrome or melanoma. The familial condition consists of several types. A patient who has dysplastic nevus syndrome and a family history of the syndrome is designated as having type B. In type C, in addition to the syndrome, the patient has a personal history of melanoma but a family history of neither the syndrome nor melanoma. Type D consists of two forms: type D1 patients have one family member with the syndrome and melanoma, whereas D2 patients have two or more relatives with the syndrome and melanoma. It is estimated that dysplastic nevi may be found in 30 to 50% of sporadic, nonfamilial melanoma patients.

Each of these types carries an increasing risk of developing melanoma. "Sporadic dysplastic nevus syndrome (type A), which occurs in 5 to 10% of the general population, raises your chances of developing melanoma by five- to sevenfold, even if you have just one dysplastic nevus," Duvic said.

The most dramatic increase in risk, however, is familial dysplastic nevus syndrome. Risk ranges from 148-fold greater for families in which type B dysplastic nevus syndrome has been identified to 500-fold in families identified with type D2. The latter was initially termed B-K syndrome by Mark H. Greene, M.D., and coworkers of the National Cancer Institute. (The initials were derived from two of the seven families studied.) These investigators noted a relationship between dysplastic nevi and the subse-
quent development of melanoma. Virtually all family members with a personal history of melanoma had dysplastic nevi, and of the 39 new melanomas that developed during the study, all occurred in patients who had dysplastic nevus syndrome. In stark contrast, of the patients who had normal skin, none developed melanoma during the course of the study. From a prevention and treatment standpoint, however, the most important finding was that the new melanomas were detected at an early, highly curable stage in their development. Thirty-six were less than 0.76 mm in diameter. Patients who have lesions of this size have virtually a 100% cure rate. Consequently, identifying dysplastic nevus is the first step in identifying patients at high risk for melanoma.

**Symptoms like bleeding or burning could be a sign that the mole is in the process of transformation.**

**Some Aspects of Treatment are Controversial**

There is no disagreement as to treatment for an individual dysplastic nevus that may be on the pathway to malignancy: local excision. However, patients with the syndrome can have more than 100 moles. Whether to excise all of them or only those that are suspicious is currently a subject of controversy, according to Duvic. “There are about as many different opinions as there are dermatologists and pathologists,” Duvic said. “And I don’t think that the truth is known yet. Removing every mole is probably unrealistic because of the amount of surgery involved and the fact that these individuals continually develop new moles. What is realistic, however, is following the nevi. If any change occurs in size, color, or shape, then local excision is called for. At M. D. Anderson we make this decision on an individual basis. Changing or suspicious moles are excised and examined microscopically. In the future, linkage of familial melanoma and dysplastic nevi to certain genes may become a possibility.”

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The disease was suspected soon after birth. On clinical examination, the infant had skeletal deformities and neuromata of the gut. The diagnosis was confirmed by calcitonin measurement of the peripheral blood, which showed a rise (rather than a fall) after 3 months. The patient underwent a thyroidectomy, which revealed the calcitonin-cell hyperplasia before tumor formation. We expect no recurrence of thyroid disease. Even though calcitonin is the most useful diagnostic marker, carcinoembryonic antigen (CEA) is a better prognostic marker. We have found that patients with a progressive increase of CEA levels have poor prognosis.

We also found that in familial MEN II with bilateral pheochromocytoma, bilateral adrenalectomy with partial preservation of the normal adrenal cortex is the treatment of choice since the patient will not be dependent on steroid hormone replacement.

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Dysplastic Nevus Syndrome Identifies Patients at High Risk for Melanoma

Accurate identification of the dysplastic nevus syndrome can play a critical role in curing melanoma. Mounting evidence suggests that dysplastic nevi are the histogenic precursors of malignant melanoma. Even if a particular dysplastic nevus does not itself become malignant, the patient still has a 7- to 70-fold increased risk of developing melanoma in some other area of the body.

"Since melanoma is curable if caught early, the bottom line is that any suspicious lesion should be removed," said Madeleine Duvic, M.D., the chief of Dermatology Section at the M.D. Anderson Cancer Center.

For this reason, Duvic and coworkers in the Dermatology Clinic pay particular attention to dysplastic nevi. "We follow patients on a regular basis—every 6 to 12 months," Duvic said. "Generally, we monitor all moles for any changes, but dysplastic nevi are particularly important because of the associated risk of melanoma. Normal moles tend to be small, brown, and uniformly colored, whereas dysplastic nevi are large and their pigmentation is variegated. Recently, Alfred W. Kopf, M.D., and colleagues at New York University defined three clinical criteria indicative of the dysplastic nevus syndrome: the presence of 100 moles or more, moles greater than 8 mm in diameter, and moles with irregular borders and variegated pigment."

Dysplastic nevi represent an intermediate stage between common acquired nevi and malignant melanoma. Common acquired nevi develop along a predictable path, beginning as 1- to 2-mm macules. As the nevus approaches 6 mm, lateral growth ceases and cells penetrate the underlying dermis. As the nevus continues to descend, the epidermal appearance becomes clinically normal. Dysplastic nevi, however, deviate from this pattern of development. These lesions range from 5 to 12 mm and usually are shades of dark brown, brown, tan, or pink. In some cases, focal areas...