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Guest editorial

Prevention and treatment of organ toxicity during high-dose chemotherapy: an overview

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By using increased doses or dose intensities of cytostatic agents, improvements in clinical outcome may be achieved in some cancer cases. However, high-dose chemotherapy may produce dose-limiting adverse reactions such as myelosuppression, neurotoxicity, cardiotoxicity, gastrointestinal toxicity, nausea and vomiting. The use of bone marrow transplantation, autologous infusion of circulating hematopoietic progenitors and hematopoietic growth factors have been shown to significantly reduce the severity and duration of the pancytopenia associated with cytostatic chemotherapy and chemoradiotherapy. In addition, recent developments in the control of nausea and vomiting with selective 5-HT_3 antagonists have improved the tolerability of chemotherapy. The antiemetic efficacy of these agents has been shown to be equivalent to combination therapy with metoclopramide plus dexamethasone in the prevention of cisplatin-induced emesis. Progress in the prevention and treatment of organ toxicity is now required, if treatment with higher doses and dose intensities of cytostatic drug treatments are to be used for the future treatment of human malignancies.

Key words: Chemotherapy, granisetron, myelosuppression, nausea, organ toxicity, vomiting.

Introduction

A review by Frei and Canellos of the effect of the dose of chemotherapeutic agents concluded that the use of the maximum tolerated dose provides the greatest opportunity for tumor response.[1] While an editorial by Henderson[2] pointed out that although the rates of achievement of complete responses using high-dose chemotherapy with bone marrow support may seem impressive, the duration of response and survival is generally disappointingly short. Also, there have been few clinical studies which have been designed specifically to evaluate the effects of varying dose intensity on response and survival.[3]

The use of high-dose regimens has been associated with a statistically significant survival advantage in three randomized clinical trials, in acute lymphocytic leukemia in children,[4] in small-cell carcinoma of the lung[5] and in testicular cancer.[6] In a randomized trial in patients with metastatic breast cancer higher response rates and better palliation were achieved by using full-dose chemotherapy.[7] Also, in trials using high-dose chemotherapy with bone marrow support higher response rates and prolonged disease-free survival have been reported in patients with malignant lymphoma,[8] breast cancer[9] and testicular cancer.[10] Finally, a number of retrospective analyses have suggested a positive correlation between dose intensity and treatment outcome in a number of human malignancies.[11]

Myelotoxicity

Although increased dose or dose intensity of chemotherapy may not always improve clinical response, it is apparent that in certain cancers these factors may be correlated with response, degree of palliation and possibly survival. In most cases the major dose-limiting toxic effect of chemotherapeutic regimens is myelosuppression. Therefore, the ability to reduce the severity and duration of drug-induced pancytopenia has considerable potential to affect the prospects of high-dose chemotherapy and chemoradiotherapy. Bone marrow transplantation (BMT) (autologous, syngeneic and allogeneic) has allowed the use of more intensive myeloablative therapies.[12–14] Infection-related morbidity and mortality, however, are high during the period of hematopoietic reconstitution. Bone marrow recovery after allogeneic BMT is generally faster than after autologous BMT but the occurrence of acute graft-versus-host-disease (GVHD) is a major limitation. T cell depletion effectively reduces the

incidence of severe forms of acute GVHD[15] but it may be associated with slower marrow recovery and more opportunistic infections.[16]

A second technique now being employed, either alone or in combination with BMT, to promote hematopoietic recovery after myeloablative therapy is the autografting of peripheral blood stem cells (PBSCs) or progenitors, which have been harvested using leukapheresis before chemotherapy. It has been reported that these cells generally induce a faster hematopoietic recovery than bone marrow autografts.[17] A third possible approach to limiting the severity and duration of drug-induced myelosuppression is the use of hematopoietic growth factors, either alone or in combination with bone marrow or PBSC reinfusion.

Studies addressing the myelotoxicity of cancer chemotherapy have demonstrated a consistently beneficial effect of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) on the severity and duration of neutropenia.[18–20] GM-CSF and G-CSF have also been shown to significantly increase the yields of peripheral blood progenitors when given prior to a leukapheresis.[21,22] When given after BMT G-CSF and GM-CSF have resulted in significantly faster recovery of leukocyte and neutrophil counts, and lower use of systemic antibiotics compared with BMT alone.[23,24] Recombinant human interleukin-3 (rhIL-3) is just beginning to be studied in patients with bone marrow failure resulting from chemotherapy.[25–27]

Patients with cancer are often anemic even before they receive cytotoxic therapy and even if their bone marrow is not affected by the disease. It has been shown that in a large group of patients with a variety of solid tumors there is an inadequate response to erythropoietin (EPO) for a given degree of anemia and that this is exacerbated by chemotherapy.[28] This suggests that inadequate EPO production may contribute to the development of anemia in patients with cancer and that replacement with exogenous EPO may be useful in the treatment of these patients.

Thus, it is now apparent that several of the known hematopoietic growth factors have effects which may contribute to a reduction of the severity and duration of myelosuppression associated with cancer chemotherapy. More studies are required to determine the full therapeutic potential of these and other cytokines in this respect. However, physiologically these molecules operate in synergistic and antagonistic ways within a complex network of mechanisms to determine the responses to infection. This indicates that much greater clinical efficacy will come in the future from combinations of these cytokines to give more appropriate increases in cell counts.[29]

Now that more effective techniques for promoting and accelerating hematopoiesis following myelosuppressive chemotherapy are being developed and refined, the use of higher doses and dose intensities of cytotoxic drugs is likely to become more widespread. However, many chemotherapeutic agents exert toxic effects on other tissues and organs often in a dose-related and sometimes irreversible fashion. Organ toxicities often reflect the delayed effects of antineoplastic agents on specific cells of an organ and have little to do with the proliferative activity of these cells.

Neurotoxicity

Neurotoxicities, including peripheral, autonomic and cranial, may be dose limiting for the vinca alkaloids (vincristine, vinblastine and vindesine). Until recently there was no treatment available to prevent these neuropathies; however, it has now been shown that glutamic acid, administered at a dose of 1.5 g daily significantly reduces vincristine-induced neurotoxicity.[30] Neurological toxicity occurring in patients treated with cisplatin is usually limited to peripheral neuropathy and ototoxicity; however, other signs including retrotubular neuritis, Lhermitte's sign, encephalitic symptoms and autonomic neuropathy have also been described in the literature.[31] The pathophysiology of cisplatin neuropathy is as yet undefined, but it is generally dose related and may not be reversible. Neuropathy is now considered to be the dose-limiting toxicity of cisplatin treatment[32] and it may result in decreased motor function and an inability of the patient to perform occupational tasks or to care for themselves.[33] Quantitative measurements of vibration perception thresholds in patients treated with cisplatin provide a relatively simple, accurate and reliable technique for the monitoring of cisplatin neuropathy.[34] Although the mechanisms by which cisplatin attacks neurons is still obscure, a number of studies have been performed using a variety of compounds as potential neuroprotective agents. Phase I studies using the sulfur-containing compound ethiofos have suggested that it may exert a neuroprotective effect without impairing the antitumor activity of cisplatin[35] and further controlled studies are ongoing. A recent study by van der Hoop *et al.*[36] has indicated that the ACTH

analog Org 2766 may prevent or attenuate cisplatin-induced neuropathy without adversely affecting the cytotoxic effect of cisplatin. Whether this neurotrophic peptide will prove to be useful in other forms of neuropathy is currently being investigated.

Cardiotoxicity

Doxorubicin and the related anthracycline daunomycin are known to be associated with cardiotoxicity. Several clinical presentations of doxorubicin-induced toxicity have been described, including a variety of atrial and ventricular dysrhythmias, a pericarditis–myocarditis syndrome, acute post-dose hypertensive reactions and chronic cardiomyopathy.[37] However, there are few early symptoms of toxicity and patients may only begin to experience the increasingly debilitating symptoms weeks or months after the last dose. As the total cumulative dose of doxorubicin is the most significant risk factor it is usually restricted to a lifetime dose of 400–500 mg/m^2 (approximately 6–8 months of therapy). Radionuclide angiography and echocardiography are useful non-invasive predictors of cardiac damage and correlate well with impending toxicity.[37,38] However, while they assist the overall care of patients receiving doxorubicin, these monitoring techniques have not dramatically diminished the problem of cardiac toxicity. Administration of the drug by prolonged rather than short continuous intravenous infusion has been shown to reduce the cardiac toxicity of doxorubicin considerably;[39] however, the standard method of administration of doxorubicin is still short intravenous infusion. The EDTA analog ICRF-187 has been shown to prevent damage to the heart from anthracyclines,[40] apparently through inhibition of the formation of strong oxidizing species by the chelation of delocalized iron within the tissues.[41]

Nephrotoxicity

The nephrotoxicity associated with cisplatin therapy used to be considered a major dose-limiting factor. However, this toxicity can now be considerably reduced by the use of a number of protective agents and procedures. The maintenance of adequate hydration and the use of a saline or mannitol diuresis has been shown to reduce urinary tract toxicity.[42] In addition, administration of WR-2721, an organic thiophosphate compound, before cisplatin treatment, has been shown to improve renal tolerance to cisplatin and may permit the use of higher doses.[35] The heavy metal-chelating agent, diethyldithiocarbamate (DDTC), when given after cisplatin has also been shown to protect against nephrotoxicity.[43] Methotrexate is commonly associated with renal toxicity. Urinary alkalinization will prevent precipitation of the drug and administration of citrovorum factor (leucovorin) will protect against nephrotoxicity.[42] Both cyclophosphamide and ifosfamide may cause hemorrhagic cystitis. The uroprotective agent mesna is administered with the latter to prevent this occurring.[44,45]

Gastrointestinal toxicity

Stomatitis or oral mucositis occurs frequently as a result of treatment with some chemotherapeutic agents including methotrexate, 5-fluorouracil, bleomycin, cytarabine, actinomycin D and doxorubicin. The condition occurs two to three times more frequently in patients with hematological malignancies such as leukemia and non-Hodgkin's lymphoma than in persons with solid tumors.[46] The incidence and severity of stomatitis are closely related to the drug dose and method of delivery, with continuous often infusion resulting in improved tolerance compared with intravenous bolus injection. In addition, a recent study by Mahood *et al.*[47] has shown that the use of oral cryotherapy considerably reduced stomatitis in patients receiving 5-fluorouracil.

Gastrointestinal disturbances including diarrhoea and constipation are common side-effects of antineoplastic therapy, depending on the drug used, and are usually mild or moderate. Diarrhoea is frequently reported as a result of treatment with 5-fluorouracil, hydroxyurea and streptozotocin, while vincristine therapy may cause constipation. These conditions are generally treated symptomatically and rarely warrant discontinuation of treatment or reduction of dose.[42]

Nausea and vomiting

Although myelosuppression is recognized by many healthcare professionals as the major dose-limiting side-effect of cancer chemotherapy, the most

distressing symptoms perceived by the patient are generally nausea and vomiting.[48] While some patients are able to cope with these symptoms others have major problems, sometimes so severe that they may refuse further cycles of potentially curative therapy.

Different cytostatic agents have varying emetogenic potential, with highly emetogenic regimens such as high-dose cisplatin causing nausea and vomiting in the majority of patients. The dose and schedule used are also important determinants of the emetogenic potential of a regimen, as cisplatin, for example, is most emetogenic when given as a high dose over a short period of time, but is better tolerated when given as a prolonged infusion or over several days.[49] However, the use of agents in combination may introduce synergistic effects on nausea and vomiting which means that the patient's experience will be worse than could be expected from that seen with the single agents. Thus, as the use of more dose-intensive regimens becomes more commonplace the effective control of nausea and vomiting will become even more important to maintain compliance and quality of life.

Three types of emesis have been characterized in patients receiving cytostatic drug treatment: (i) post-treatment/acute vomiting which occurs in the first 24 h after treatment; (ii) delayed emesis, which may occur up to several days after treatment, depending on the regimen; and (iii) anticipatory emesis, which occurs when nausea and vomiting are not adequately controlled in the first cycles.[50] The latter is a conditioned response and tends to be refractory to treatment. The pattern of acute nausea and vomiting which follow the administration of emetogenic agents varies considerably. For example, with cyclophosphamide, these events may not appear until 18 h after chemotherapy. Therefore, with combination regimens synergistic effects and temporal differences may produce a complex response. With cisplatin-based regimens nausea and vomiting can be delayed for several days after chemotherapy. Such delayed emesis has not responded to conventional antiemetics so its mechanism of action may be different for acute episodes. Adverse experience of nausea and vomiting in the acute phase can lead to the development of anticipatory nausea and vomiting. This conditioned response can be initiated by anything associated with treatment and is often triggered by the sight of the hospital or the nurse who administered previous cycles. This can be particularly difficult for the patient and can affect compliance further.

Nausea is experienced more often than vomiting,[51] is the side-effect most frequently reported by patients and the one they find hardest to tolerate. Nausea may persist for some time after the cessation of vomiting[52] and its control should be a priority because of its role in the etiology of conditioned anticipatory events.[53]

Antiemetic therapy

Until recently antiemetic therapy has relied on combinations of drugs (some being included to counteract the adverse effects of others) used in a somewhat empirical fashion. The classes of compounds used include phenothiazines, butyrophenones, benzodiazepines, corticosteroids, cannabinoids, substituted benzamides (e.g. metoclopramide) and antihistamines. This has often been defined in a somewhat empirical fashion with few controlled trials to determine the optimum dose and method of administration.[54] Often the basis for their use is not based on a sound mechanism of action. The side-effects of these agents, which may be additive where a combination is used, include sedation (for benzodiazepines, phenothiazines, butyrophenones and antihistamines), extrapyramidal symptoms (for phenothiazines, high-dose metoclopramide and butyrophenones), hallucinations (for cannabinoids), and mental changes, muscle wasting and fluid retention (for corticosteroids). These adverse effects can significantly affect the patient's quality of life and may necessitate additional periods of hospitalization. Metoclopramide, given in high doses, is still one of the most commonly used antiemetics, and the recognition that the antiemetic effect of the drug operated through the 'M' or 5-HT_3 receptor subtype[55] led to the development of the 5-HT_3 antagonists, such as granisetron, tropisetron and ondansetron. Granisetron and other 5-HT_3 antagonists have been shown to control early cytostatic drug-induced emesis, both as prophylactic and as intervention agents.

Treatment with granisetron has been shown to be equivalent to the combination of metoclopramide plus dexamethasone in the prevention of cisplatin-induced emesis, producing a complete response (no vomiting and no or only mild nausea) rate of 70% during the first 24 h.[55] With moderately emetogenic regimens, granisetron was significantly better than the conventional combination of chlorpromazine plus dexamethasone, with 68% of granisetron-treated patients having a complete response compared with 47% with the comparator.[57] Granisetron was shown to have similar

efficacy to the conventional combinations of alizapride plus dexamethasone and metoclopramide plus dexamethasone during 5 days of fractionated chemotherapy, with significantly greater control during the initial 24 h.[58] Granisetron maintains its efficacy at approximately 67–70% over repeat cycles of chemotherapy, whilst response to standard antiemetics is known to diminish after multiple cycles.[59]

Ondansetron, the first selective 5-HT_3 receptor antagonist to become available, has been shown to possess better antiemetic efficacy and lower toxicity than high-dose metoclopramide in cisplatin-induced emesis.[60] Complete protection from vomiting was obtained in 40–45% of patients. When combined with dexamethasone the efficacy of ondansetron can be significantly increased[61] and has been shown to be superior to metoclopramide plus dexamethasone plus diphenhydramine. Complete protection from vomiting was obtained in 79 versus 60% of patients after day 1 and was maintained up to 3 days after cisplatin treatment.[62]

Treatment with tropisetron in patients with cisplatin-induced emesis resulted in a good response for nausea and vomiting in 83 and 88% of courses, respectively, with complete protection in 45 and 66% of courses.[63] When compared with antiemetic therapy using metoclopramide in combination with lorazepam, tropisetron therapy was significantly superior ($p < 0.001$) in controlling both acute and delayed symptoms.[63] In patients with insufficient control of emesis whilst receiving standard antiemetics, tropisetron was significantly superior in producing complete control of vomiting during the first 24 h ($p < 0.001$).[64]

Tolerability of selective 5-HT_3 receptor antagonists is good with headache and constipation, the most frequently reported adverse events.[65]

Of particular note is that treatment with selective 5-HT_3 antagonists has not been associated with extrapyramidal effects, a particularly distressing effect reported with dopamine antagonists. Thus, granisetron and other selective 5-HT_3 antagonists should help to make chemotherapy more tolerable for patients and thereby promote compliance with treatment regimens and perhaps permit the use of higher dose intensities of drugs, which could lead to improved responses to treatment.

Summary

Thus, it appears that for certain tumors increases in dose and/or dose intensity of cytostatic drug treatment may result in improved clinical outcome. Three types of adverse response to cytostatic chemotherapy which may be dose limiting are myelosuppression, specific organ toxicity, and nausea and vomiting. BMT, autologous infusion of circulating hematopoietic progenitors and the use of hematopoietic growth factors have been shown to significantly reduce the severity and duration of the pancytopenia which is associated with cytostatic chemotherapy and chemoradiotherapy. Also, with the development of selective 5-HT_3 antagonists such as granisetron, a breakthrough can be achieved in the control of nausea and vomiting that will reduce the subjective side-effects associated with higher doses of chemotherapy to a considerable extent. Although some progress has been made in the area of prevention and treatment of organ toxicity, for some drugs reduction of dosage/dose rate or cessation of therapy are still the only techniques for prevention of toxicity. If higher doses and dose intensities of cytostatic drug treatments are to be used in the future techniques for the prevention of organ toxicity need to be further developed.

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