'.....Which Makes Life Even Better'

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Antiemesis

Post-chemotherapy vomiting used to be the major obstacle for patient acceptance of chemotherapy. This is one of the most feared toxicity, from the patient's point of view. Cytotoxic drugs can be classified according to their emetic potential. Highly emetogenic drugs include cisplatin, paraplatin, darcarbazine and anthracyclines. Psychological factors also contribute to the onset and severity of post-chemotherapy vomiting. One tends to associate chemotherapy with vomiting. Once it has started anticipatory vomiting is significant.

Before 1990 the available antiemetic agents were: promethazine, chlorpromazine, metoclopramide, diphenhydramine, aided by lormetazapam and dexamethasone. These were only minimally effective, especially against highly emetogenic drugs.

The H3-antagonists appeared after 1990[1]. Ondansetron, Tropisetron and Graniesetron became available. Together with dexamethasone these H3-antagonists reduced acute emesis i.e. vomiting on the day of chemotherapy significantly. They have little effect on delayed vomiting i.e. vomiting after the first day of chemotherapy. They are also effective against radiation-induced vomiting.

The latest in antiemesis involved the drug aprepitant, a selective, high-affinity antagonist at substance P/neurokinin 1 (NK_1) receptors. The drug crosses the blood-brain barrier and occupies NK_1 receptors in the brain. Aprepitant acts in the CNS to inhibit emesis induced by cytotoxic chemotherapy, including both the acute and delayed emesis.

Efficacy of aprepitant in patients receiving highly emetogenic chemotherapy was established in 2 controlled clinical studies[2,3] comparing a regimen containing aprepitant in combination with a $5\text{-}HT_3$ antagonist (ondansetron) and a corticosteroid (dexamethasone) with a standard regimen containing ondansetron and dexamethasone alone. In these studies, 63-73% of those receiving the regimen with oral aprepitant or 43-52% of those receiving the standard regimen experienced a complete response (i.e., no emetic episodes and no use of rescue therapy) from 0-120 hours after treatment with cisplatin. In the acute phase (0-24 hours) after cisplatin treatment, 83-89% of patients receiving the aprepitant regimen or 68-78% of those receiving the standard regimen experienced a complete response. In the delayed phase (25-120 hours) after cisplatin treatment, 68-75% of patients receiving the aprepitant regimen or 47-56% of those receiving the standard regimen experienced complete response.

The first dose is given orally at least one hour before the start of chemotherapy. The timing is important to allow the NK_1 receptors in the chemotherapy trigger zone (ctz) in the brain stem to be occupied by the drug. Both acute and delayed vomiting are now reduced significantly. So much so that now cisplatin can be used with relative ease. Chemotherapy induced vomiting is no longer feared by the patient, and the physician.

Osteoporosis and endocrine therapy

Osteoporosis is frequently associated with hypogonadal states, in women deprived of oestrogen and men androgen. Osteoporosis is associated with morbidities such as hip fractures, spine fractures, bone pain and kyphoscoliosis.

Known remedies in such situations include increasing dietary intake of calcium (+/- supplements of vitamin D), weight bearing exercise and oral bisphosphonates.

Anti-oestrogens play an important role in the treatment of endocrine-receptor positive breast cancer, in both early and metastatic breast cancers. Known anti-oestrogens include tamoxifen and the aromatase inhibitors anastrozole, letrozole and exemestane. Aromatase inhibitors, which inhibit oestrogen synthesis in postmenopausal patients, are used more and more often, especially in the adjuvant setting. Aromatase inhibitors increase the risk of osteoporosis, which in any case is already more prevalent in postmenopausal patients.

Recently clinical trials have demonstrated that using the parenteral bisphosphonate zoledronic acid can help prevent bone loss and even increase bone density during adjuvant therapy with aromatase inhibitors in early breast cancer.

The 'Zometa-Femara Adjuvant Synergy Trial'[4] (Z-FAST) tested the efficacy in postmenopausal patients. Patients receiving adjuvant letrozole were randomly assigned to receive either upfront or delayed-start zoledronic acid (4 mg intravenously every 6 months). The delayed group received zoledronic acid when lumbar spine (LS) or total hip (TH) T score decreased to less than -2.0 or when a nontraumatic fracture occurred. The upfront and delayed groups each included 301 patients. At month 12, LS BMD was 4.4% higher in the

upfront group than in the delayed group (95% CI, 3.7% to 5.0%; P < .0001), and TH BMD was 3.3% higher (95% CI, 2.8% to 3.8%; P < .0001). In the upfront group, mean serum N-telopeptide and bone-specific alkaline phosphatase concentrations decreased by 15.1% (P < .0001) and 8.8% (P = .0006), respectively, at month 12, whereas concentrations increased significantly in the delayed group by 19.9% (P = .013) and 24.3% (P < .0001), respectively. With 1 year of follow-up, results of the primary end point of the Zometa-Femara Adjuvant Synergy Trial (Z-FAST) indicate that upfront zoledronic acid therapy prevents bone loss in the LS in postmenopausal women receiving adjuvant letrozole for early-stage breast cancer.

A similar conclusion can be drawn in premenopausal breast cancer patients receiving endocrine treatment. In a randomised trial[5], endocrine treatment without zoledronic acid led to significant (P < .001) overall bone loss after 3 years of treatment (BMD, -14.4% after 36 months; mean T score reduction, -1.4). Overall bone loss was significantly more severe in patients receiving anastrozole/goserelin (BMD, -17.3%; mean T score reduction, -2.6) compared with patients receiving tamoxifen/goserelin (BMD, -11.6%; mean T score reduction, -1.1). In contrast, BMD remained stable in zoledronic acid-treated patients.

Gonadotropin-releasing hormone (GnRH) agonists decrease bone mineral density and increase fracture risk in men with prostate cancer. GnRH agonists are now commonly used for androgen ablation for men with prostate cancer, both metastatic and non-metastatic.

In a 12-month study[6], 40 men with nonmetastatic prostate cancer who were receiving a GnRH agonist and had T scores more than -2.5 were randomly assigned to zoledronic acid (4 mg intravenously on day 1 only) or placebo. BMD of the total hip decreased by 1.9% +/- 0.7% in men assigned to placebo and increased by 0.7% +/- 0.5% in men assigned to zoledronic acid (P = .004). Similar between-group differences were observed for the femoral neck and trochanter. Serum N-telopeptide, a marker of osteoclast activity, decreased significantly after zoledronic acid treatment.

Thus a single treatment with zoledronic acid significantly increased BMD and durably suppressed serum N-telopeptide levels for 12 months. Annual zoledronic acid may be a convenient and effective strategy to prevent bone loss in hypogonadal men.

In these two common cancers amenable to hormonal manipulation, adding a bisphosphonate improves the quality of life by reducing skeletal morbidities.

References

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