

KEY TOPICS IN SUPPORTIVE CARE: CONCLUSIONS AND PRACTICAL IMPLICATIONS

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CONFLICT OF INTEREST: DISCLOSURE

- I am a member of the Advisory Board on aprepitant for MSD
- I have been a speaker for MSD Italy on the prophylaxis of chemotherapy-induced emesis
- I am conducting research sponsored by MSD on the prophylaxis of emesis with aprepitant

JAW OSTEONECROSIS

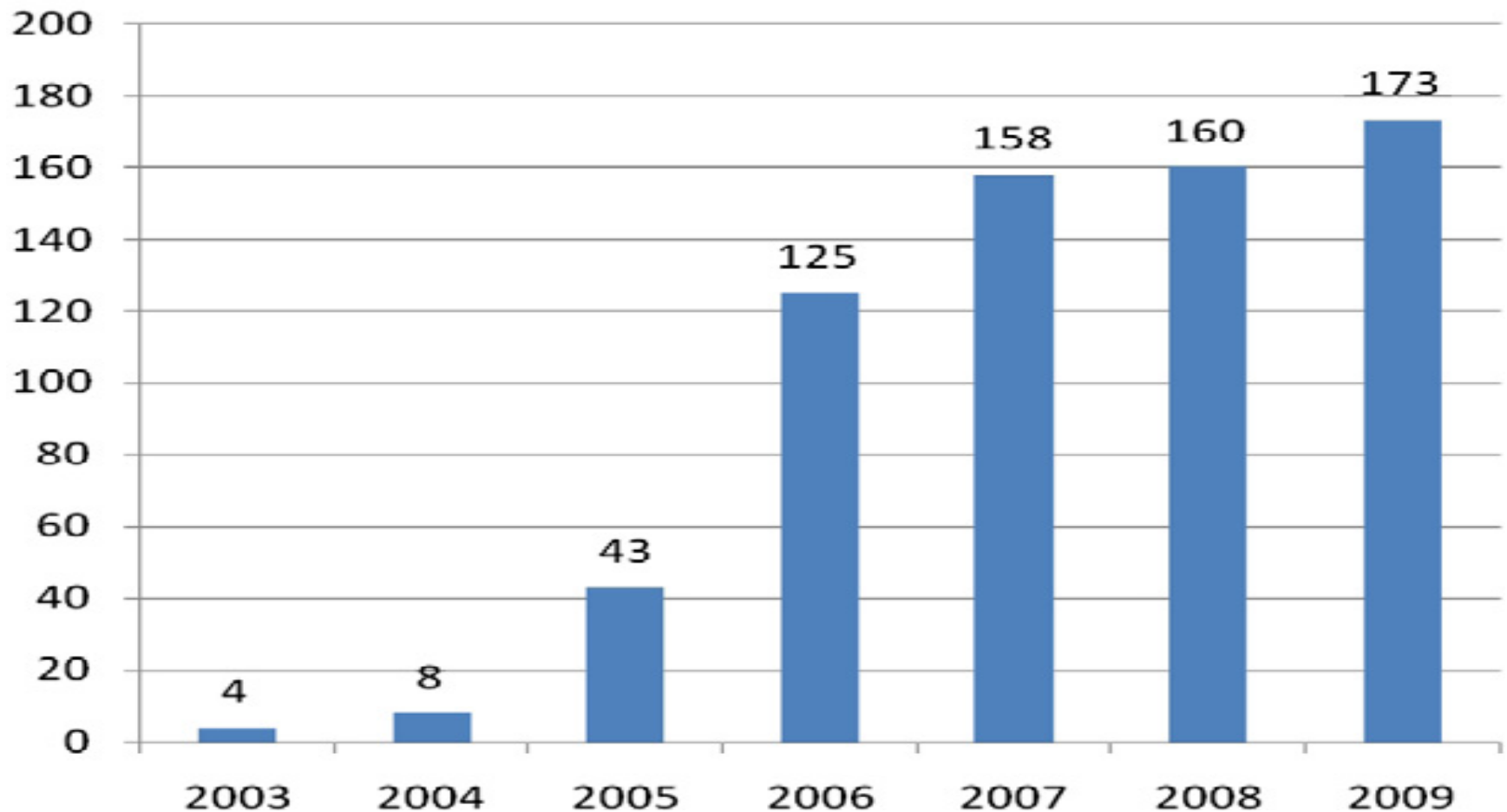
Number of publications on BRONJ from 2003 to 2009

(Kuhl S, et al. Oral Oncol 2012,

<http://dx.doi.org/10.1016/j.oraloncology.2012.03.028>)

Numerical Distribution

n = 671



GRADE OF EVIDENCE OF 176 STUDIES

- 1 study level Ia (meta-analysis of several RCT)
- 8 studies level Ib (at least one RCT)
- 9 studies level IIa (non-randomized CT)
- 25 studies level IIb (at least one other type of quasi-experimental study)
- 101 studies level III (descriptive studies, cohort or case control studies)
- 32 reports level IV (by panel of experts, etc.)

INCIDENCE OF BRONJ

- In 47 studies (64% were retrospective studies) the mean incidence of BRONJ after **intravenous administration** was 7% (0-27.5%).
- In 9 studies the mean incidence of BRONJ after **oral administration** was 0.12 (0% - 4.3%)

INCIDENCE: LIMITATIONS

- The incidence is difficult to determine because of differences in definition, differences in type, dosage and duration of the bisphosphonate treatment, differences in disease and status of the disease. Furthermore, there are some mild self-resolving cases not identified.
- Only the establishment of large-scale population registries of pts prescribed bisphosphonates (and denosumab) with long term follow-up could provide definitive answers

OUTCOMES OF CONSERVATIVE AND SURGICAL TREATMENT

- 66 of 103 pts (64.1%) **receiving a conservative treatment** + antibiotics had healing of their lesions, 6 (5.8%) showed an improvement and 8 pts (7.8%) had refractory BROMJ
- 141 (58.8%) of 240 pts **receiving radical surgery** + antibiotics had healing of the lesions, 47 (19.6%) an improvement and 10(4.2%) pts had refractory BROMJ

OUTCOMES: LIMITATIONS

- Although the success of both treatments seems similar this comparison is biased because surgery is often performed in cases with extended necrotic bone and this is sometimes associated with worse general health conditions influencing the surgical result
- In any case, the difficulties in treating BONJ highlight the importance of implementing preventive measures in clinical practice

CONCLUSIONS

- Large scale population registries are necessary to evaluate the incidence of bisphosphonate (and denosumab)- related jaw osteonecrosis.
- There is consensus that the standard goal for controlling jaw osteonecrosis is to prevent it
- Randomized clinical trials are necessary to identify the best strategies to repair the exposed bone once bone necrosis has developed

HEPATITIS B & C

HEPATITIS AND IMMUNOSUPPRESSION

- **Pts with HCV infection** rarely present significant clinical sequelae after immunosuppressive therapy
 - Literature limited to a few case series and case reports
 - Hepatitis “flares” can occur especially in pts receiving rituximab

HEPATITIS AND IMMUNOSUPPRESSION

- Pts infected with HBV may have significant hepatitis “flares” following immunosuppressive therapy which can result in hepatic failure, need for liver transplant and occasionally death.

MANAGEMENT OF HBV IN PTS RECEIVING CHEMOTHERAPY

- Identification of currently or previously infected pts with appropriate requesting and interpretation of hepatitis B serology
- All pts with chronic hepatitis B should be started on antiviral prophylaxis before starting CT and for a period of 6-12 months after completed CT

MANAGEMENT OF HCV IN PTS RECEIVING CHEMOTHERAPY

- Screen pts with HCV Ab, if positive do PCR
- Current HCV treatments are interferon-based and poorly tolerated

THE CLINICAL PRACTICE

- A survey was sent to all Australian oncologists to determine the clinical practice with regard the HBV screening in pts with solid tumors: 63% answered.
- Fifty-three percent of medical oncologists screen for HBV, but only 19% screen all patients.
- Oncologists who did not screen most commonly cited inadequate evidence for a benefit of screening (72%).

Day FL, et al. JOP 2011; 7: 141-47

THE CLINICAL PRACTICE

- A survey was sent to American Medical Association registered oncologists assessing HBV screening practices.
- In all, 265 responses were received. Responders screen for HBV as follows: **never: 20%, only in the presence of abnormal liver biochemistries: 30%**, risk factors or history of hepatitis: 38%.

Tran TT, et al. Aliment Pharmacol Ther 2010; 31, 240–246

COST-EFFECTIVENESS OF UNIVERSAL HBV SCREENING

- A pharmacoeconomic study has been carried out to evaluate the cost-effectiveness of the recommended universal HBV screening in pts with solid tumors
- **Universal HBV screening is not cost-effective** ($\leq$ \$50,000 Australian dollars): for adjuvant breast cancer pts (\$88,224/LY, 13% probability of being cost-effective), palliative metastatic NSCLC pts (\$1,344,251/LY, 0%), or pooled (all) patients (\$149,857/LY, 1%)

Day FL, et al. JCO 2011; 29: 3270-77

THE CLINICAL PRACTICE

- Recently, a decision model was developed to compare the clinical outcomes and costs of three screening strategies for patients with lymphoma before R-CHOP:
 - screen all patients for HbsAg,
 - screen patients at high risk for HBV reactivation
 - screen no one.
- The results shown that **screening all patients for HBV reduces the rate of HBV reactivation (10-fold) and is less costly** than screening only high-risk patients or screening no patients

Zurawska U, et al. JCO 2012; DOI:10.1200/JCO.2011.40.7510

OTHER PROBLEMS

- The current recommendations are based on limited evidence (most studies are retrospective or, if prospectively designed, compared the effect of prophylactic antiviral therapy against historical controls).
- There are no large prospective trials evaluating homogeneous cohort of patients and most of the trials included patients treated with heterogeneous cytotoxic schedules.

OTHER PROBLEMS

- The mortality related to the HBV reactivation is not generally reported and this does not allow us to clearly understand the real benefit of prophylaxis in terms of improvement of survival.
- Prospective clinical trials comparing the efficacy of lamivudine versus other more potent antiviral agents such as entecavir, adefovir and tenofovir are needed.

INFLUENZA VACCINATION

RECOMMENDATION

- There is evidence that patients with cancer receiving chemotherapy are able to respond to influenza vaccination, and because this intervention is safe, inexpensive, and widely available, vaccination for seasonal influenza and the novel H1N1 strain is indicated.

Pollyea DA et al. JCO 2010; 37: 2481-90

INFLUENZA VACCINATION

- The CDC recommend annual vaccination with inactivated viral vaccine for immunosuppressed hosts including cancer pts.
- Unfortunately, this recommendation has been scarcely implemented in clinical practice.
- A survey in 196 cancer pts showed that 30% of pts reported never receiving the influenza vaccine and only 7% have been informed about vaccination by their oncologists (Yee SS, et al. J Support Oncol 2010; 8: 28-34)

INFLUENZA VACCINATION

- The most beneficial timing of vaccination in oncology pts has not been well studied. **Administering the vaccine between cycles of chemotherapy is recommended**, while pts taking oral or biologic-targeted therapy could continue therapy without interruption for the vaccination.
- In a recent study patients on chemotherapy have significantly lower responses to influenza virus vaccination compared with healthy controls. **Vaccination early (day 4) during the chemotherapy** cycle induces better responses than does vaccination at day 16 of the cycle (*Meerveld-Eggink A, et al. Ann Oncol 2011; 22:2031-35*)

INFLUENZA VACCINATION

- It would be useful to vaccinate pts at least 2-4 weeks before the start of seasonal influenza (late December)
- To increase the immune response (seroprotection and seroconversion) multiple doses of vaccine should be administered to cancer pts

THROMBOSIS AND CANCER

MANAGEMENT OF VTE IN CANCER PTS: ESMO GUIDELINES [Mandalà M, Ann Oncol 2011; 22 (Suppl 6): 85-92]

Prevention of VTE:

- **Major abdominal or pelvic surgery:** a prophylaxis with LMWHs (i.e.; enoxaparin 4000 U or dalteparin 5000 U sc. Day) or UFH (5000 U TID) is recommended
- **Hospitalized cancer pts:** a prophylaxis with UFH, LMWH or fondaparinux is recommended in pts bedridden with an acute medical complication
- **Cancer pts receiving adjuvant CT:** not recommended

MANAGEMENT OF VTE IN CANCER PTS: ESMO GUIDELINES [Mandalà M, Ann Oncol 2011; 22 (Suppl 6): 85-92]

Prevention of VTE:

- Consider LMWH, aspirin or adjusted-dose warfarin (INR ~ 1.5) in myeloma pts receiving thalidomide plus dexamethasone or plus CT
- Ambulatory pts receiving palliative CT for locally advanced or metastatic disease: extensive routine prophylaxis is not recommended, but may be considered in high-risk ambulatory cancer pts.

STUDY RESULTS

- **Two studies in advanced pancreatic cancers** enrolling 123 and 312 patients, compared prophylaxis with dalteparin or enoxaparin versus no prophylaxis. In both studies venous thromboembolism was reduced from 25.0% to 3.5% and from 9.9% to 1.2%.
- More recently **two large randomized double-blind studies compared nadroparin or semuloparin versus placebo** in patients with different advanced cancers who were starting chemotherapy. The rate of venous thromboembolism was 2.0% in 1150 patients with nadroparin versus 3.9% with placebo and 1.2% in 3212 patients with semuloparin versus 3.4% with placebo. The rate of major bleeding events was 0.7% versus 0% and 1.2 versus 1.1, respectively.

AMBULATORY PATIENTS RECEIVING CHEMOTHERAPY: PREVENTION OF VTE

- The identification of ambulatory cancer **patients** submitted to chemotherapy that are **at high risk of venous** thromboembolism is essential to avoid unnecessary exposure to prophylaxis to patients at lower risk of venous thromboembolism.

KORANA'S SCORE (4660 patients)

Pts characteristics

SCORE

site of cancer

very high risk (stomach, pancreas) 2

high risk (lung, lymphoma, gynecologic, bladder, testicular) 1

prechemotherapy leukocyte count ($> 11,000$ mmc) 1

prechemotherapy platelet count ($> 350,000$ mmc) 1

anemia (< 10 g/dL) or use of red cell growth factors 1

body mass index > 35 Kg/m² 1

Low risk patients (score 0), intermediate risk (score 1-2); high risk (score 3 or more)

CONCLUSIONS

- In ambulatory cancer patients submitted to chemotherapy thromboprophylaxis is not mandatory and should remain not recommended due to the low absolute reduction rate of venous thromboembolism (1.9% and 2.2% in the two studies) and the risk of major bleeding (0.7 and 0.1%).
- A prospective study to determine the efficacy of primary thromboprophylaxis in high-risk patients identified using Korana's score is ongoing. The results of this study are eagerly awaited.

MANAGEMENT OF VTE IN CANCER PTS: ESMO GUIDELINES [Mandalà M, Ann Oncol 2011; 22 (Suppl 6): 85-92]

Prevention of VTE:

- **Central venous catheters:** not recommended

PROPHYLAXIS FOR PATIENTS WITH CVC

- **In four recent studies (3 double-blind)** the incidence of symptomatic CVC-related venous thromboembolism is generally low (about 3-4%) and there is no statistically significant difference between patients undergoing and patients not undergoing prophylaxis.
- **A no blind study** carried out in 420 patients receiving low molecular weight heparin or warfarin or no prophylaxis showed a catheter-related thrombosis in 8.1% of pts receiving anticoagulant drugs and 14.8% receiving no prophylaxis, a difference statistically significant.

PROPHYLAXIS FOR PATIENTS WITH CVC

- This study is not a blind study, which is important to avoid selection bias, and it is a monocentric study requiring 11 years to be completed
- Further studies should be carried out to evaluate the efficacy of an anticoagulant prophylaxis in patients with CVC

PROPHYLAXIS OF VTE IN CLINICAL PRACTICE

Several studies showed **underuse of available prophylaxis of VTE.**

- In a review of almost 200.000 charts of US medical pts at moderate or high risk of VTE who were admitted to the hospital, appropriate prophylaxis was done in only 34% (*Amin A et al. J Thromb Haemost 2007; 5: 1610-16*)
- In Switzerland prophylaxis was not provided to 40% of 257 cancer pts admitted to the hospital before the onset of acute VTE (*Kucher N et al Ann Oncol 2010; 21: 931-35*)

TAKE HOME MESSAGE

- Important progress has been achieved in the prophylaxis of jaw osteonecrosis, hepatitis B reactivation, influenza and venous thromboembolism

BUT

There is an absolute necessity to transfer the results achieved by research to clinical practice