normal p53 gene would induce the tumour cells to apoptose. Alternatively if the p53 is normal then the level of the p53 expression would enable the cells to become more chemo-sensitive to agents such as cisplatin.

Infections and cancer

402 POSTER

Haematological colony-stimulating factors (CSF) in febrile neutropenic patients. A systematic review of the literature with meta-analysis

T. Berghmans[1], M. Paesmans[1], J.J. Lafitte[2], A.P. Meert[1], C. Mascaux[1], E. Steels[1], F. Vallot[1], J.P. Sculier[1]. [1] *Institut Jules Bordet, Internal Medicine, Bruxelles, Belgium;* [2] *CHU Calmette, Pneumology, Lille, France*

Purpose: To assess the role of G-CSF and GM-CSF in the treatment of febrile neutropenic cancer patients, we conducted a systematic review of the randomised trials published as full papers on this topic.

Methods: A methodological evaluation using a specifically designed quality scale was performed before meta-analysis. The effect of CSF on mortality was measured by the odds ratio, estimated in each individual trial. A combined odds ratio was obtained using the method described by Peto.

Results: Eleven trials were eligible of which 8 were meta-analysable (962 febrile neutropenic episodes). The median quality score for the 11 pooled trials was 58.3% (range: 33.3%-68.8%). The lack of significant quality difference ($p = 0.36$) between positive (CSF more effective) and negative trials allowed us to perform a quantitative aggregation of the individual studies results. No advantage on mortality due to febrile neutropenia was detected for the use of CSF with an odds ratio of 0.69 (95% CI 0.42-1.15; $p = 0.98$). The odds ratio was 0.61 (95% CI 0.34-1.09; $p = 0.43$) in the G-CSF subgroup and 1.05 (95% CI 0.36-3.05; $p = 0.99$) in the GM-CSF subgroup. No other meaningful quantitative aggregation could be performed due to the lack of adequate data in the publications.

Conclusions: On the basis of this review, we cannot recommend the routine use of G-CSF or GM-CSF in established febrile neutropenia.

403 POSTER

Infectious complications after autologous peripheral blood progenitor cell transplantation (PBPCT) in breast cancer (BC) patients

A. Zambelli, G.A. Da Prada, L. Velutti, L. Ponchio, G. Robustelli della Cuna. *Salvatore Maugeri Foundation, Medical Oncology Division, Pavia, Italy*

We retrospectively analyzed the infectious complications in 148 patients, median age 46 yrs (range 23-64), who underwent high dose chemotherapy and PBPC autologous support plus G-CSF, for breast cancer both in primary (pBC) and metastatic setting (mBC). Mobilizing regimen and myeloablative treatments varied according to the setting of pts. PBPC mobilization was obtained with high-dose CTX plus G-CSF regimen in the 102 pBC pts while Paclitaxel+Epirubucin plus G-CSF regimen was used in the 46 mBC pts.

Myeloablation included high-dose alkylators-based regimen: TioTepa + LPAM for pBC, and CTX + TioTepa + Mitoxantrone in the mBC setting.

Pts were isolated in a germ-free room after myeloablative treatment and received antimicrobial iv prophylaxis with quinolone, fluconazolo and acyclovir. Median time for neutrophils (ANC>0.5x10e9/L) and platelets (>20x10e9/L) recovery were respectively 10 and 9 days. One hundred and twenty eight patients (86%) developed fever (>38.5 °C, median 4 days, range 2-10); bacteremia occurred in 28 pts (22%): 23 of them (81%) had Gram positive while 5 (19%) had Gram negative bacterial infections. There were no fungal infections or infection-related deaths.

The development of bacteremia was strongly associated with grade IV mucositis ($P<0.001$; odds ratio 11.8) and with neutropenia ANC<0.1x10e9/L lasting more than 5 days ($P<0.01$; odds ratio 4.5), without any significant difference between the 2 setting of pts. Febrile women received a second line antimicrobial therapy with amikacin, ceftazidime and teicoplanin. In most of these cases the severity of the infections was moderate and no life-threatening infectious complications were observed. In our experience, the severe but short-lasting neutropenia and mucositis are significantly associated with incidence of bacterial infections after PBPCT but, with appropriate anti-infective treatment, these infections can be managed without sequelae.

Angiogenesis

404 POSTER

X rays affect the extracellular matrix in a way that favours both normal and tumour-induced angiogenesis

E. Giannopoulou[1], P. Katsoris[2], M. Hatziapostolou[1,2], D. Kardamakis[3], E. Kotsaki[1], C. Polytarchou[1], A. Parthymou[1], S. Papaioannou[1], E. Papadimitriou[1]. [1] *University Of Patras, Pharmacy, Patras, Greece;* [2] *University Of Patras, Biology, Patras, Greece;* [3] *University Of Patras, Medicine, Patras, Greece*

Purpose: Previous studies, using the chicken embryo chorioallantoic membrane (CAM) model of in vivo angiogenesis, have shown that X rays have an antiangiogenic effect. In the present study, we tried to clarify some of the mechanisms through which X rays regulate angiogenesis.

Methods: Apoptosis was studied using DNA fragmentation and acridine orange staining. The amounts of the proteins of the ECM and their mRNAs were quantitated using image analysis of the corresponding Western blots and RT-PCRs respectively. An ELISA test has been used to quantitate the amounts of integrin alpha1 β3 and zymography was used for MMP-2. Tissue localization of ECM proteins or tumor cells implanted onto CAM, has been performed by immunohistochemistry and histochemistry, using paraffin sections of CAMs.

Results: Apoptosis was evident within 1-2 h, but not later than 6 h after irradiation. Fibronectin, laminin, collagen type I, integrin alpha1 β3 and MMP-2 protein amounts were all decreased 6 h after irradiation. In contrast, collagen type IV, which is restricted to basement membrane, was not affected by irradiation of the CAM. There was a similar decrease of gene expression for fibronectin, laminin, collagen type I and MMP-2, 6 h after irradiation. The levels of mRNA for integrin alpha1 β3 and collagen type IV were unaffected up to 24 h after irradiation. The decrease in both protein and mRNA levels was reversed at later time points and 48 h after irradiation, there was a significant increase in the expression of all the genes studied. When C6 glioma tumour cells were implanted on irradiated CAMs, there was a significant increase in the angiogenesis induced by tumour cells, compared to that in non-irradiated CAMs.

Conclusion: Although X rays initially have inhibitory effect on angiogenesis, their action on the ECM enhances normal and tumour-induced vessel formation.

405 POSTER

The angiogenic role of harp, a novel growth factor

E. Papadimitriou[1], A. Polycratis[2], M. Heroult[3], G. Kokolakis[2], J. Courty[3], P. Katsoris[2]. [1] *University of Patras, Department of Pharmacy, Patras, Greece;* [2] *University of Patras, Department of Biology, Patras, Greece;* [3] *Universite Paris Val de Marne, Laboratoire de Recherche sur la Croissance Cellulaire, la Reparation et la Regen, Paris, France*

Purpose: HARP (Heparin Affin Regulatory Peptide) is a 18 kDa secreted protein with distinct lysine-rich clusters within both the NH2- and COOH-terminal domains. It is a growth factor that exhibits a high affinity for heparin and is localized in the extracellular matrix, where it interacts with glycosaminoglycans. In the present work, we studied the angiogenic action of HARP and two peptides representing the termini of the molecule (HARP residues 1-21 and residues 121-139), which are rich in lysine and have high affinity for heparin.

Methods: Angiogenic action was studied in the in vitro models of matrigel and collagen gels. As an in vivo model, we used the chicken embryo chorioallantoic membrane (CAM). Quantification of the vessel networks was performed with image analysis of digitized images. Migration studies were performed using Boyden chamber tests. Human recombinant HARP was expressed and purified from E. coli.

Results: HARP induces migration and stimulates endothelial cells to form tubular, capillary like structures in several in vitro models of angiogenesis (matrigel, collagen and fibrin gels). Using the in vivo model of chicken embryo CAM, we found that HARP has an angiogenic effect. This biological action was seen whether or not HARP has the three amino acid extension of the N terminus region and the exact role of those amino acids remains unclear. The two HARP peptides tested are also angiogenic in most of the assays used. They both stimulate in vivo angiogenesis and in vitro endothelial cell migration and tube formation on matrigel.

Conclusions: We conclude that HARP has an angiogenic activity and its NH2 and COOH termini seem to play an important role.