ABSTRACTS

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257 Opening Ceremony - P. Gourmelon

The French radiation accident experience: emerging concepts in radiation burn and ARS therapies and in brain radiopathology

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Accidental overexposures are rare and unique events and are of the greatest importance for lessons to be learned in terms of radiopathology and medical management for diagnosis and treatment. Several victims of industrial radiation source accidents which occurred in the past in different countries (Georgia 1997, 2002, Peru 1999, Poland, 2001, Chile 2005, Belgium 2006, Senegal 2006, and Tunisia 2008) were successively treated in France in Percy Hospital for very severe skin radiation burns. Different types of treatments were applied and new therapeutic approaches were designed in order to improve the final outcome. Another accident occurred in a stereotaxic radiosurgery unit in Rangueil Hospital (Toulouse, France) between April 2006 and April 2007. This accident was the cause of a high level of brain complications among a cohort of 145 patients treated for benign or malignant tumours of the brain. The experience feedback of these accidents revealed emerging concepts in several fields of radiopathology. The Chilean accident illustrated the advantage of dosimetry-guided surgery in the treatment of radiation burn, the accidents of Chile, Senegal and Tunisia demonstrated the benefits of cell therapy in the treatment of severe skin injuries, the Senegal and the Belgium accidents demonstrated the interest of a new approach in the treatment of the hematopoietic syndrome and the French radiosurgery accident provided new information concerning the radiosensitivity of brain structures and cranial nerves.
Lessons to be learned in the field of treatment of radiation burn. The therapeutic management of severe radiation burns remains a highly puzzling and challenging issue. In case of profound and painful ulcerations or necrosis with ischemic process the lesion should be excised (ulcerectomy, necrectomy) and the wound bed should be covered with a rotation flap and/or a good quality, full thickness skin graft. This conventional surgical treatment often fails to prevent unpredictable and uncontrolled extension of the radiation-induced necrotic process. This is due

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to several causes: the very frequent delay in the recognition of the radiological nature of the lesions, the dynamic feature of radiation burn due to the occurrence of serial inflammatory waves, the difficulty to delineate excision of radiation lesions on account of apparently healthy irradiated tissues, the possible expansion of the necrosis after each surgical excision and the long, fragile and uncertain healing of these radiation injuries involving muscles, blood vessels and skin. The radiation lesion often becomes uncontrolled and the final option is a last surgical act leading to a very high morbidity and disability. In the Peruvian accident (1999), the recurrence of successive inflammatory waves and uncontrolled superinfections required iterative excisions leading to amputation and mutilations (Peru 1999). In another case (Georgia, 2002), the wide size of the radiological lesion in surface and in depth involved a very long surgical treatment (500 days) where 4 successive excisions with skin autografts allowed a partial healing of the peripheral part of the radiological lesion. The final cicatrisation of the centre of the radiation burn was obtained only with a vascularised tissue flap (omentum). A similar treatment was also applied in a case from the Poland accident (2001). In the most recent accidents new therapeutic strategies were planned to shorten the duration of the treatment and to improve its efficiency. One of the unsolved issue in the classical surgical treatment of the radiation burn is the size of the excision surgery, the actual limits of the lesion being unknown. In the Chile accident, it was possible to perform a physical dosimetric reconstruction to guide the surgical excision. Physical dose reconstruction with numerical methods requires perfect knowledge of position and distance of the source and the duration of the exposure. The most subjective key parameter of the dose reconstruction is the duration of exposure which was pretty well quantified in this accident. A dose reconstruction mapping was obtained from a personalized voxelized phantom generated from the tomodensitometric images of the victim. The isodose of 20 Gy was used as a guide value for the surgical excision (10 cm in diameter and 5 cm in depth) in the apparently healthy tissues surrounding the moist desquamation area. This accident illustrated that dose reconstruction is a useful tool to guide the surgical gesture and this approach should be prioritized when the accidental circumstances are well defined. In the 3 recent accidents (Chile, Senegal, Tunisia) an innovative therapeutic approach combining surgery with autologous mesenchymal stem cell (MSC) transplantation was applied. MSC are defined as pluripotent cells capable of proliferating extensively and able to give rise to skeletal tissue and marrow stroma cells. The aim of the MSC therapy was to deliver to the site of the lesion trophic factors able to favour the healing of the impaired tissue. Using successive local administrations of MSC combined with rotation flaps and skin autografts it was possible to obtain a favourable outcome of radiological lesions located in various anatomical areas (fingers, hands, arm, and buttock) and due to radiation doses up to 50 Gy. MSC could favour the healing process through the secretion of cytokines and trophic factors that may have counteracted the local inflammation. This novel multidisciplinary therapeutic approach may be of clinical relevance for improving the medical management of severe localized irradiations. It may open new prospects in the field of radiotherapy complications.

Lessons to be learned in the field of treatment of the Acute Radiation Syndrome (ARS).

The classical treatment of the hematopoietic syndrome of the ARS depends on the evaluation of damage to the bone marrow. If the damage is reversible then the treatment is a substitution and supportive therapy or a stimulation therapy by cytokines. If the damage to bone marrow is irreversible the treatment is stem cell transplantation. In past accidents, several ARS patients were treated with stem cell transplanatation in the days following exposure, provided that the irradiation dose was estimated to be high. The experience feedback of these stem cell transplanatations suggests that the radiation dose window in which the stem cell therapy may be useful is narrow and require a lethal marrow injury without any evidence of injury to other organs that may lead to a multiple organ dysfunction syndrome. In order to propose a consensus guideline in the treatment of the hematopoietic syndrome, two consensus conferences were organized in 2003 and 2005. Based upon this experience feedback, it was proposed the following criteria for proposing a stem cell transplantation: a persistent bone marrow aplasia on day 21 post-irradiation, without any sign of an endogenous haematopoiesis, no sign of digestive and/or pulmonary severe disease, and a biological/biophysical dosimetry suggesting a radiation dose over 10 Gy with a minimal gradient of dose. In two recent radiation accidents (Belgium 2006 and Senegal 2006), two victims presented some sign of an hematopoietic syndrome. In the Senegal case, the hematopoietic syndrome was treated with cytokine injections approximately one month post-irradiation and resolved in few days. With the Belgium case, which was detected 3weeks after irradiation, the hematopoietic syndrome was severe. However, due to uncertainty on both the radiation dose and the heterogeneity, it was choose to start a cytokine treatment on day 28 post-irradiation, in order to stimulate a possible residual hematopoiesis. An hematopoietic recovery was then observed during the following week. These results demonstrate that the radiation-induced hematopoietic syndrome is not an emergency for stem cell transplantation, and that it is an absolute requirement to obtain evidence of an irreversible damage to the bone marrow before proposing a stem cell transplantation. These results also demonstrate that a cytokine treatment should be efficient, even if started more than 4 weeks after irradiation, thus confirming the validity of the proposed approach by these consensus conferences.

Lessons to be learned in the field of treatment of the brain radiopathology.

The stereotactic radiosurgery accident that took place in France between 2006 and 2007was linked to underestimation of a scatter factor in a dedicated LINAC system. 32 patients with unilateral acoustic neurinomas were overexposed. The experience feedback of this accident on this cohort of patients allowed assessing a dosimetric-related index for prediction of cranial nerve deficits. This index was derived from dose volume histograms and should allow sparing trigeminal nerve during radiosurgery of vestibular schwannomas. During the median follow-up period of 12 months, the actuarial rate of trigeminal neuropathy in patients was 31% which is undoubtedly higher to those reported in the literature and is directly related to the accidental overexposure. The prediction index of the cranial neu-

ropathies was derived from the dose volume histograms of the cisternal part of the trigeminal nerve which was manually segmented on T2 weighted MR acquisitions. None of the patients who underwent less than 8 Gy to 50% of the nerve volume developed trigeminal neuropathy. In conclusion, the trigeminal nerve in its cisternal course should be a key risk organ to take into account in the planning treatment of sterotactic surgery of neurinomas. This preliminary result will have to be confirmed at the end of a 48 months follow-up.