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INFLUENCE OF HISTOLOGICAL SUBTYPES ON THE PROGNOSIS AND SURVIVAL OF THE CHILDHOOD OSTEOSARCOMA (OS).

J García-Foncillas, P Barona, C Azcona, P León, L Sierrasesúmaga.

Departament of Pediatric Oncology. Clínica Universitaria de Navarra. Facultad de Medicina. Pamplona. Spain.

From 1982 to 1992, 70 patients with pathology proven, previously untreated OS, were treated preoperatively with intra-arterial cisplatinum 40 mg/m^2, and Adriamycin 20 mg/m^2 iv, q.o.d. times three, every three weeks for three cycles. Resection of the involved and adjacent healthy bone was performed subsequently and functional prosthesis was implanted. Treatment was continued thereafter for twelve months with a modified T10 (Rosen protocol). There were 41 females and 29 males, mean age 14 (4.6-23 yr). Tumor location was femur 37, tibia 23, humerus 5, fibula 4, and pelvis 1. At the moment of diagnosis 65 patients had localized disease and 5 patients had pulmonary metastases. Pathologic studies indicated the next histological subtypes: 48 osteoblastic OS, 14 chondroblastic OS, 6 fibroblastic OS, and 2 telangiectasic OS (14 chondroblastic vs 56 nonchondroblastic). RESULTS: For a time of ten years of follow-up, according with Kaplan-Meier method, the overall survival is 71.66 ± 6.6 % (3454 days). At this moment 53 patients are alive without disease, 3 alive with disease, 10 patients dead for progressive disease, and 4 dead for toxicity. The influence of the different histological subtypes has been analysed in relation with the prognosis. Chondroblastic versus Nonchondroblastic histological subtypes showed the next features: higher rate of local recurrence (60 % vs 13.3 %, $p < 0.001$), higher incidence of metastatic disease (50 % vs 23 %, $p < 0.04$), and lower survival without progression of disease (42.86 ± 16.53 vs 89.29 ± 5.14, $p < 0.003$). In conclusion, we consider chondroblastic histological subtype as negative prognostic factor that must be reflected on the treatment evaluation.

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HIGH VALUE OF DRUG INTENSITY (D.I.) AND SERIC INTENSITY (S.I.) IN OSTEOGENIC OSTEOSARCOMA. RESULTS OF DD1 PROTOCOL AT 5 YEARS.

N. DELEPINE, G. DELEPINE, V. SUBOVICI, H. CORNILLE, S. ALKALLAF, JC DESBOIS.*

Oncologic Pediatric Service - Robert Debré Hospital
48 boulevard Sérurier - 75019 PARIS - FRANCE

As the correlation between the seric level and the given dose/sqm of MTX is not linear, we decided to test the S.I of MTX (Pilot Study DD1 protocol). We defined the S.I as the mean value of Cmax obtained at the end of the MTX infusion in $10.^{-6}$ mol/l/week.
MATERIAL AND METHODS : 21 patients (p), 7 to 28 y. with non metastatic limb OS (11 inf femur, 7 tibia, 2 humerus, 1 fibula) received HDMTX immediatly after diagnosis, the 1st course adapted to age and other courses (3 to 4) to individual pharmacokinetics in order to obtain a 1 000 µmol/l peak at the end of the 6th hour infusion. En bloc resection was performed between the 30th and 35th day after biopsy, followed by BCD. Good responders (GR) received T 10 B and bad responders (BR) 6 cycles of 2 MTX + IPA (x 4) or BCD (x 2). Local radiotherapy was applied to BR with marginal resection.
RESULTS. *Pharmacological datas*, mean total dose MTX is 192 g/sqm. Total DI is 5 g/sqm/week, total SI is 590 µmol/l/week. **Preop DI is 13 g/sqm/week, preop SI 1150 µmol/l/week.** *Tolerance* of MTX was good. Hematologic toxicity of IPA was notable. No lethal side effect was noted. *Functional results* following EMSOS criterias were rated excellent 8, good 8, fair 2, bad 3 (secondary amputated for infection). *Oncologic results* : 13 p out of 21 were GR, 2 p relapsed at 12 and at 24 m, are in 2nd CR from 4 & 3 y. At a median FU of 66 m (min 42/max 84) the actuarial overall survival and DFS are 100% at 5 y with no late relapse. **The EFS is 91% at 5 y with a plate from 2 y.**
CONCLUSION : The comparison of these promising results to our previous study, shows **that S.I of MTX is the best prognostic factor of good histological response and of DFS.**

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AGE AND DOSE INTENSITY (DI) OF VCR AND ACT D ARE SIGNIFICANT PROGNOSTIC FACTOR IN EWING'S SARCOMA (ES).

N. DELEPINE, G. DELEPINE, H. CORNILLE, V. SUBOVICI, JC DESBOIS*

University Oncologic Pediatric Service - Hospital Robert Debré
48 boulevard Sérurier 75019 PARIS - FRANCE

MATERIEL & METHODS : 32 patients (p) with ES non pretreated were included in DD2 and DD21 pilot studies from 86. In 18 p volume was > 100 cm^3, in 14 p age > 21 y, 5 p were initially metastatic. All p received 3 courses of induction chemotherapy (CT) : CPX 150 mg/sqm x 7 + THPADR at day 8 with a week rest. Surgery was systematic after this induction with an en bloc extratumoral resection when possible (limbs and girdles) and large curetage in vertebral locations. Postop CT alternated 6 courses of IPA (IFX 6 gr/sqm, CDDP 125 mg/sqm THPADR 35 mg/sqm), 3 courses of CPX-THP (as induction) 12 courses of VCR (1,4 mg/sqm max 2 mg), 6 courses of ActD (2 mg/sqm max 2 mg), 6 months of CPX 2,5 mg/kg/24 h.
RESULTS : With a FU of 50 months 23 p are DFS, 9 relapsed. Actuariel DFS is 68% at 5 y. Analysis shows that initial metastasis remain a bad pronostic factor (DFS 40% at 5 y). Initial tumoral volume, locations and biologic factors are no more pronostic factors in this study. Age remains a major bad pronostic factor : half adult p. relapsed versus only 11% $p < 21$ y. Nevertheless multifactorial analysis showed that pronostic value of age in this study is highly correlated with dose intensity of drugs. In the group of p whose total body surface was > 1,3 m², the intensity of dose of VCR and ActD was significantly lower because of the habitual use of max dosages for these drugs and most of these p. relapsed : in the contrary in our studies, intensity dose of CPX, IFX, CDDP, THP ADR, are not different in the group of p. DFS and in p. in evolution in disease (ED). Between these 2 groups VCR DI decrease in ED, p is significant ($p < 0,001$) and ACTD DI decrease in ED, p is significant ($p < 0,002$).
CONCLUSION : **The better prognosis of ES in children (89% EFS at 5 y in our studies) than in adults, is correlated with DI of ACT D and VCR.**

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EFFICACY OF DIFFERENT APPROACHES FOR THE TREATMENT OF MYELODYSPLASTIC SYNDROME (MDS) IN CHILDREN

D Nikitin, E Petrova, N Klubovskaya, M Ivanovskaya, N Adametskaya, E Boichenko, T Melnikova, T Zharinova
Petrov Research Institute of Oncology & Children's City Hospital N°1, Sankt-Petersburg, Russia

Treatment of patients (pts) with MDS represents a complex problem in pediatric oncohematology. There have been few studies on this field. We have analyzed the survival of 32pts <14y with various MDS subtypes (RA -11 RAEB -8, RAEB-t -2, JCML -7, CMML - 4) therapeutic regimens applied. The following treatment was used: low dose AraC (LDA)-Group(Gr)1, 8pts; LDA+intensive chemotherapy (CT) -Gr2, 6pts; CT alone -Gr3, 2pts; prednisone and supportive care -Gr4, 7pts. Children with hypoplastic MDS were treated with immunosuppressive therapy (IST) including ATG, high dose methylprednisolone and cyclosporine A -Gr5, 9pts. The probability of survival at 2y was 56±20% in Gr1, 42±22% in Gr2, 0% in Gr3, 69±±19% in Gr4 and 52±20% in Gr5. These data demonstrated that large proportion of children with MDS may benefit from nonaggressive treatment (i.e.LDA and IST). Further trials of this regimens are warranted.