# MULTICENTER COOPERATIVE PHASE 3 STUDY FOR THE TREATMENT OF RECENTLY DIAGNOSED MULTIPLE MYELOMA: A RISK BASED STRATEGY

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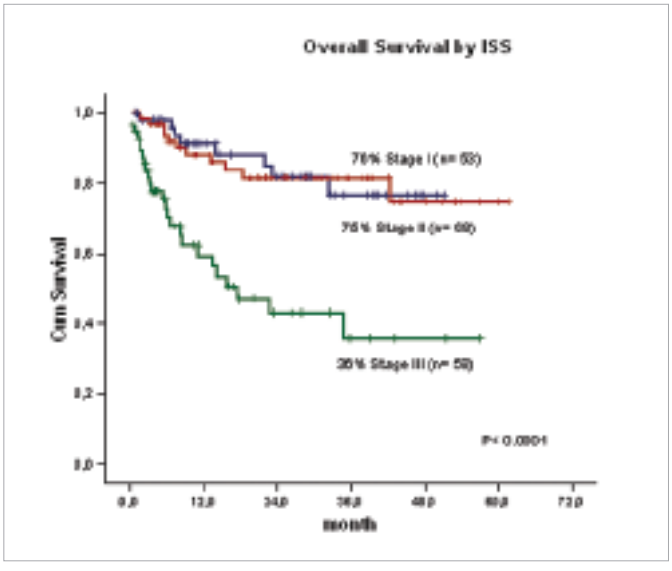
Our main objectives are:

To validate stratification by risk, proposing therapeutic strategies that vary in intensity, to evaluate the role of thalidomide in association with dexamethasone (low risk) or DCEP (high risk) as a consolidation scheme after the autologous transplant. This is a prospective, comparative multicentric, randomized and open study with two treatment groups, in accordance with risk stratification. Patients who do not show cytogenetic alterations involving chromosome 13 (analyzed by the FISH technique and conventional cytogenetics) and/or have a beta-2-microglobulin dose of 2.5 mg/l or less will be considered low risk patients, while high risk will be defined as those showing the presence of both alterations above. Treatment for the low risk group will consist of three chemotherapy cycles with the VAD scheme (vincristine, doxorubicin, and dexamethasone) administered at the outpatient clinic, followed by mobilizing the hematopoietic stem cells of the peripheral blood with cyclophosphamide (4g/m$^2$) and G-CSF (10 g/kg/day). After collecting a minimum of 4 x 10$^8$ cells CD34+/Kg of weight, the patient will be submitted to an autologous transplant, whose conditioning regime will be 200 mg/m$^2$ of melphalan. After D+100 of the transplant, patients will be randomized into two consolidation groups: thalidomide (200 mg/d) + dexamethasone (40 mg/d for 4 days once a month), in a total of 12 months, or dexamethasone (40 mg/d for 4 days, per month), in a total of 12 months. If there is relapse or progression of the disease, the patients will receive a second autologous transplant. Those who do not have enough cells collected (previous collection or new mobilization) will receive three cycles of monthly chemotherapy with the DCEP scheme (dexamethasone 40 mg/day for 4 days, cyclophosphamide 400 mg/m$^2$ for 4 days, cisplatin 10 mg/m$^2$ for 4 days and etoposide 40 mg/m$^2$ for 4 days) with or without thalidomide (200 mg/d), depending on whether or not they have used it before. For the high risk group, treatment will differ after the autologous transplant. Patients under 60 and identical HLA donors will receive a non-myeloablative allogenic transplant, and their conditioning regime will be the melphalan scheme (70 mg/m$^2$ /day for 2 days) and fludarabine (30 mg/m$^2$ /day for 4 days). As consolidation, these patients will receive infusions of lymphocytes from the donor on days D+60, 90, and 120 if they do not present acute GvHD. For patients above 60 or without compatible HLA donor, a second autologous transplant will be offered with the same conditioning scheme as the first. After D+100 of transplant, patients treated with the second autologous transplant will be randomized to receive chemotherapy with DCEP every three months, during a year (totaling four cycles) in one arm, and DCEP with thalidomide 200 mg/d for a year in the other consolidation arm. This study will last five years and shall include no less than 71 low risk patients, in each maintenance arm. Response rates, global survival and survival free from the disease will be analyzed in both groups, just as patients quality of life will be evaluated in the various phases of the protocol.



## SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

ISS was highly predictive of prognosis in a Brazilian study in myeloma patients.

In 2003 the International Myeloma Foundation (IMF) group proposed a new International Prognostic Index (ISS). MM Brazilian group recently published in a retrospective analysis the utility of ISS in Brazil. This study presents the use of ISS in a multicentric prospective clinical trial performed in Brazil and its impact on survival. From October 2003 to January 2008, 229 untreated patients under 71 years old were enrolled in a prospective study developed in Brazil. All patients signed the informed consent and the protocol was approved by the Ethical committees. 190 patients were analyzed. 11 did not present data for ISS classification. At the end, 179 patients were included in this analysis, 53 (29.6%) ISS I, 68 (38%) ISS II and 58 (32.4%) ISS III; 93 (51.9%) were male and 86 (48.1%) female; the median age was 55 y (27 – 70) for the whole group; 38 (21.2%) Durie-Salmon II and 141 (78.8%) DS III. DS I were excluded from this clinical protocol. 132 out of 179 (77.6%) had 13q deletion analysis. For all patients, hematological (including BM), biochemistry and radiological tests/analyses were performed. The treatment was based on three phases: debulking with 3-6 VAD followed by high dose cyclophosphamide (4g/$m^2$) for mobilization plus ASCT and consolidation using dexamethasone with or without thalidomide. The statistical analysis was made by Chi-Square, Kaplan-Meier curves (log-rank test) and ANOVA. ISS I distributed by DS system showed DS II 15/53 (28%) and DS III 38/53 (72%); ISS II had DS II 15/53 (28%) and DSIII 38/53 (72%); ISSII had DSII 19/68 (28%) and DSIII 49/68 (72%) and ISSIII had DSII 4/57 (7%) and DS III 53/57 (93%) ($p< 0.0001$). Concerning the presence of 13q deletion, 12/36 (33%) ISS I, 16/51 (31%) ISS II and 17/45 (37%) ISS III (NS). The median observation time for whole group was 22 months and for alive patients 24 mo (1-62). 44 out of 179 (24%) died, most of them in VAD phase due to progression. 135/179 (76%) are alive, ISS I 45/53 (85%), ISS II 57/68 (84%) and ISS III 33/58 (57%) ($p< 0.001$). The OS in 60 mo by ISS was 76%, 75% and 36% for ISS I, II and III, respectively ($p< 0.0001$). The EFS in 60 mo by ISS was 38%, 32% and 10% for ISS I, II and III, respectively ($p< 0.0001$). The ANOVA showed significant difference for plasma cells bone marrow infiltration, creatinine and hemoglobin levels ($p< 0.0001$). The importance of ISS at diagnosis is emphasized due to its high capacity to discriminate among groups with low cost. In fact, the authors know that it is at the present moment too early to present any clinical trial results, for the protocol is still ongoing.

## MAIN PUBLICATIONS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