

MEETING COVERAGE

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1 Superiority of melphalan-prednisone (MP) + thalidomide over MP and autologous stem cell transplantation in the treatment of newly diagnosed elderly patients with multiple myeloma.

T. Facon, J. Mary, J. Harousseau, F. Hugué, C. Berthou, B. Grosbois, B. Anglaret, A. Azzedine, P. Rodon, on behalf of the Intergroup Francophone du Myélome, and A. Peny

A combination of melphalan and prednisone (MP) has been the standard treatment regimen for elderly patients with multiple myeloma. In May 2000, a multi-institutional team of French researchers initiated a trial (IFM 99–06) in patients aged 65–75 years with multiple myeloma. A total of 447 patients were randomized to three arms: 196 patients received the standard MP regimen (12 courses at 6-week intervals); 125 received MP plus thalidomide (Thalomid, Celgene; at maximum tolerated dose, <400 mg/day); and 126 received high-dose melphalan followed by autologous stem cell transplantation (VAD × 2, CTX 3 g/m², and 2 courses of melphalan 100 mg/m²). At the median follow-up of approximately 37 months, it was found that patients receiving thalidomide had significantly longer progression-free survival: 27.6, 17.1, and 19.4 months for the MP plus thalidomide, the MP alone, and the MP plus transplantation groups, respectively. The difference in progression-free survival times between the MP alone and MP plus transplantation groups was not statistically significant. The median overall survival times were 53.6, 32.2, and 38.6 months in the MP plus thalidomide, MP alone, and MP plus transplantation groups, respectively. The rate of side effects was higher in the group receiving thalidomide; 12% and 30% of patients experienced deep-vein thrombosis (DVT) and peripheral neuropathy, respectively. DVT was seen in 5% and 6.5% of patients in the MP alone and MP plus transplantation groups, respectively, and neuropathy was not seen in these groups. Dr. Thierry Facon, the lead researcher, said, “The results

of MP plus thalidomide were so superior that enrollment in the study was stopped so that everyone who was receiving MP alone could have thalidomide added to their treatment.” For more commentary from Dr. Facon on this research, please see *Advances in LLM* on page 501.

2 Mutations of KIT tyrosine kinase gene predict relapse in adult patients with core binding factor acute myeloid leukemia: A Cancer and Leukemia Group B study

P. Paschka, G. Marcucci, A. S. Ruppert, K. Mrózek, H. Chen, R. A. Kittles, T. Vukosavljevic, D. Perrotti, R. A. Larson, and C. D. Bloomfield

Core binding factor (CBF) acute myeloid leukemia (AML) consists of two cytogenetic subtypes of AML: t(8;21)(q22;q22) and inv(16)(p13q22), commonly abbreviated as t(8;21) and inv(16), respectively. This form of AML is found in approximately 15–18% of AML patients, and it is associated with a somewhat more favorable outcome. High-dose cytarabine given for at least three courses is the recommended treatment for CBF AML due to its effectiveness. Nevertheless, approximately 50% of patients relapse within 5 years. As a result, research has been undertaken to define markers to identify patients at high risk of relapse, who might benefit from alternative therapies. Dr. Peter Paschka and colleagues examined KIT mutations of exons 17 (mKIT17) and 8 (mKIT8) as such markers. Previous research showed that mKIT17 was adversely associated with outcome in patients with t(8;21) but not in those with inv(16). Both mutations of KIT are associated with abnormally activated KIT protein, which promotes proliferation of leukemia cells. Blood and bone marrow samples were collected from 110 patients with CBF AML and were analyzed for mutations of the KIT gene. Among patients with inv(16), 10 had mKIT17, 3 had concurrent mKIT8, and 8 had solely mKIT8; among patients with t(8;21), 9 had mKIT17, 2

with concurrent mKIT8, and 2 had solely mKIT8. Both mKIT17 and mKIT8 mutations were associated with significantly higher rates of recurrence. Patients with inv(16) had recurrence rates of 56% and 29% for those without and with the KIT mutations, respectively. Patients with t(8;21) had recurrence rates of 70% and 36% for those with and without the KIT mutations, respectively. Dr. Paschka commented, "If confirmed in larger trials, these findings will have a significant impact on therapeutic approaches for patients with CBF AML. One approach would be to add drugs targeting the abnormally activated KIT protein to current therapeutic approaches for patients with these mutations. Another would be to consider more aggressive therapy at the beginning of treatment, such as stem cell transplant." Other therapeutic options include tyrosine kinase inhibitors, such as imatinib (Gleevec, Novartis) or PKC412 (Novartis).

LBA3 Phase III randomized trial of sunitinib malate versus interferon- α as first-line systemic therapy for patients with metastatic renal cell carcinoma

R. J. Motzer, T. E. Hutson, P. Tomczak, M. D. Michaelson, R. M. Bukowski, O. Rixe, S. Oudard, S. T. Kim, C. M. Baum, and R. A. Figlin

Renal cell carcinoma (RCC) accounts for approximately 85% of all cases of kidney cancer. The standard treatment for RCC is either interferon- α or interleukin-2, but these immunotherapies are associated with low response rates. Based on earlier research, sunitinib (Sutent, Pfizer) was approved as a second-line therapy for advanced RCC after treatment with the standard immunotherapies had failed. The present phase III trial evaluated sunitinib as a first-line treatment in metastatic RCC, and it was found that sunitinib in this setting was associated with improved progression-free survival and response rates in comparison to the standard immunotherapies. The trial randomized 750 patients (median age = 60 years), 375 each to sunitinib or interferon- α . No patients had received previous chemotherapy, but 90% had previously undergone surgery. Sunitinib was administered at a dose of 50 mg orally once per day for 4 weeks, followed by 2 weeks off, and interferon- α was administered for 6 weeks as a subcutaneous injection at a dose of 9 million units [MU] given three times weekly. Median progression-free survival lengths were 47.3 and 24.9 weeks for sunitinib and interferon- α , respectively. The objective response rate by third-party assessment was 24.8% and 4.9% for sunitinib and interferon- α , respectively. Side effects included

fatigue and reduced blood counts, but overall, the drug was tolerated better than interferon- α , with rates of withdrawal due to adverse events in each arm of 8% and 13%, respectively. Lead author Dr. Robert J. Motzer, declared, "As a result of this trial, we believe sunitinib will become the new standard of care for advanced RCC." Researchers plan to continue to follow the patients to determine the differences in quality of life, fatigue levels, and overall survival between the groups.

LBA4 A phase 3, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma

G. Hudes, M. Carducci, P. Tomczak, J. Dutcher, R. Figlin, A. Kapoor, E. Staroslawska, T. O'Toole, Y. Park, L. Moore.

Temsirolimus (Wyeth) inhibits mammalian target of rapamycin (mTOR), a signaling protein involved in the regulation of cell growth and angiogenesis. A multicenter, randomized phase III trial evaluated temsirolimus as a first-line treatment for high-risk patients with advanced RCC. The trial had three arms, temsirolimus alone, interferon- α alone, and a combination of the two. Previous studies showed that patients with RCC who had progressed with prior treatments could benefit from temsirolimus, with the therapy sometimes causing tumor regression. It was noted that even patients with highly advanced tumors and short life expectancies benefited from temsirolimus therapy. All patients enrolled in the present study had advanced, metastatic RCC as well as poor prognosis as determined by blood cell count and number of metastases; the patients were required to have not had any previous systemic therapy. The temsirolimus-alone arm (25 mg administered intravenously [IV] once per week) included 209 patients, the interferon- α arm (≤ 18 MU administered subcutaneously [SC] 3 times per week) included 207 patients, and the combination arm (temsirolimus 15 mg IV once per week and interferon- α 6 MU SC 3 times per week). The median overall survival was 10.9, 7.3, and 8.4 months, respectively. Typically, patients with advanced RCC have overall survival lengths of less than 6 months. The rates of deaths were approximately equal among the three groups, and adverse events were generally less prevalent in the temsirolimus group, consisting mostly of asthenia, anemia, and dyspnea. Temsirolimus, because of its mechanism of action, was also associated with rashes and increased blood glucose levels,

but these side effects were not severe and were manageable. Future research will investigate the optimal method of administration of this agent as well as whether benefits can be conferred on patients through combination or sequential dosing.

LBA527 First mature analysis of the Intergroup Exemestane Study

R. C. Coombes, R. Paridaens, J. Jassem, C. J. Van de Velde, T. Delozier, S. E. Jones, E. Hall, L. S. Kilburn, C. F. Snowden, and J. M. Bliss, for the Intergroup Exemestane Study

Postmenopausal women with early-stage breast cancer who began taking exemestane (Aromasin, Pfizer) after 2–3 years of tamoxifen therapy following initial treatment were found to have a 15% lower risk of death than those who continued on tamoxifen. Exemestane inhibits aromatase, an enzyme necessary for estrogen production. In a randomized trial comparing 5 years of therapy with either adjuvant tamoxifen alone or tamoxifen for 2–3 years followed by exemestane if disease-free, recurrence of breast cancer was reduced, as were rates of metastasis and contralateral recurrence, by exemestane therapy. A total of 2,352 and 2,372 postmenopausal women were assigned to receive exemestane after tamoxifen or tamoxifen alone. The median follow-up was 4.8 years. Patients who received exemestane after tamoxifen had a 24% lower risk of recurrence, new breast cancer, or death from a non-breast cancer cause than women who received only tamoxifen. Metastasis risk was reduced by 17% and contralateral breast cancer incidence was reduced by 44% in the exemestane after tamoxifen group as compared to the tamoxifen-alone group. Tamoxifen alone was associated with higher incidences of blood clots or gynecologic problems such as uterine cancer, polyps, or vaginal bleeding, but exemestane following tamoxifen was associated with a slightly higher rate of bone fractures. Rates of heart attack, stroke, and angina were similar between these groups. Lead author Dr. Raoul C. Coombes said, “These results show that switching to exemestane after 2–3 years of tamoxifen is safe and can improve the cure rate in postmenopausal women with breast cancer.” Abstract 554 (Lønning et al) reported that vitamin D deficiency may

worsen the bone loss associated with exemestane. Vitamin D and calcium supplementation is recommended for postmenopausal women receiving this drug as well as other aromatase inhibitors, such as anastrozole (Arimidex, AstraZeneca) and letrozole (Femara, Novartis).

4502 Efficacy of lapatinib in patients with high tumor EGFR expression: Results of a phase III trial in advanced renal cell carcinoma

A. Ravaud, J. Gardner, R. Hawkins, H. Von der Maase, N. Zantl, P. Harper, F. Rolland, B. Audhuy, J. Machiels, and I. El-Hariry

Lapatinib (Tykerb, GlaxoSmithKline) is an orally active, reversible inhibitor of epidermal growth factor receptor (EGFR) and ErbB2 tyrosine kinases. Unlike sunitinib or sorafenib (Nexavar, Bayer), which are antiangiogenic agents, lapatinib inhibits the EGFR pathway, which promotes tumor growth and proliferation. A randomized, open-label phase III trial of lapatinib versus hormone therapy (megestrol acetate or tamoxifen) was undertaken in patients with advanced RCC that did not respond to standard immunotherapy. Lapatinib was shown to retard cancer growth and improve survival, with the most favorable responses seen in patients whose tumors expressed high amounts of EGFR. A total of 207 patients with advanced RCC were randomized to receive hormonal therapy and 209 patients were randomized to receive 1,250 mg/day of lapatinib for a median of 12 weeks. The median age of patients was 61 years, and 94% of patients had previous nephrectomy. Overall survival and time to progression did not differ significantly between the groups. However, among 241 patients whose tumors produced high amounts of EGFR, time to progression was 15.1 weeks in the lapatinib group versus 10.9 weeks in the hormone-therapy group; overall survival was 46 weeks and 37.9 weeks, respectively. Common side effects were rash (44% vs 3% in the lapatinib and hormone groups, respectively) and minor or moderate diarrhea (40% vs 3% in the lapatinib and hormone groups, respectively). Lapatinib is thus considered a safe new treatment option for patients with RCC that overexpressed EGFR who have failed prior therapy. Follow-up is ongoing.

5011 Efficacy of a quadrivalent HPV (types 6/11/16/18) L1 virus-like particle vaccine against vaginal and vulvar pre-cancerous lesions: a combined analysis

J. Paavonen, for The FUTURE II Study Group

Research shows that a vaccine against human papillomavirus (HPV) developed to prevent cervical cancer can also help to prevent vaginal and vulvar cancers. Annually, 6,000 cases of vulvar or vaginal cancers are diagnosed in the United States, and HPV is associated with 75–100% of vulvar malignancies in young women. Because treatment to prevent progression is difficult, research has been conducted into prophylactic therapy.

A combined analysis of over 18,000 women aged 16–26 years from Asia, Europe, and North and South America enrolled in three randomized, placebo-controlled trials showed that the vaccine prevented 100% of vulvar and vaginal precancers related to HPV. Subjects were randomized to either quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine (Gardasil, Merck) or placebo. Types 6 and 11 HPV are associated with cancer, whereas types 16 and 18 are linked to anogenital warts. Vaccination occurred at day 1 and months 2 and 6. Genital tract specimens were obtained on day 1 and at intervals of 6–12 months thereafter, up to 48 months. In the placebo group, after an average of 2 years of follow-up, there were 24 histologically confirmed cases of HPV-related grade 2 or 3 vulvar or vaginal neoplasia, whereas there were no cases reported in the vaccinated group.

5507 Postoperative concurrent radiochemotherapy versus radiotherapy in high-risk squamous cell carcinoma of the head and neck: Results of the German phase III trial ARO 96-3

R. Fietkau, C. Lautenschläger, R. Sauer, J. Dunst, A. Becker, M. Baumann, T. Wendt, K. Grünschow, C. Hess, V. Budach, H. Iro

A German randomized phase III trial assessed the efficacy of radiochemotherapy with cisplatin plus 5-fluorouracil versus radiotherapy alone in patients with postoperative high-risk squamous cell carcinomas of the head and neck. High-risk disease was defined as three or more involved lymph nodes, extra-capsular disease, and/or microscopically involved mucosal margins of resection. In the past, it has been noted that tumors frequently recur in patients

despite resection and irradiation. The trial randomized 440 patients, 214 received radiotherapy at a dose of 66 Gy/33 Fx/6.6 weeks and 226 patients received the same dose plus cisplatin 20 mg/m² and 5-fluorouracil 600 mg/m² on days 1–5 and 29–33. The researchers noted 5-year locoregional control, progression-free, and overall survival rates of 88.6% (±2.4%), 62.4% (±4.4%), and 58.1% (±4.6%), respectively, for the combination-therapy group, compared to rates of 72.2% (±3.7%), 50.1% (±4.0%), and 48.6% (±4.4%), respectively, for the radiotherapy-alone group. The incidence of distant metastases was similar between the groups. Grade 3 toxicities (eg, mucositis and leukopenia) were more frequent in the combination-therapy group, but the researchers considered the levels to be acceptable. The combination therapy was considered effective in comparison to radiotherapy alone in this population.

7001 Efficacy and safety of sunitinib in previously treated, advanced non-small cell lung cancer: preliminary results of a multicenter phase II trial

M. A. Socinski, S. Novello, J. M. Sanchez, J. A. Brahmer, R. Govindan, C. P. Belani, J. N. Atkins, H. H. Gillenwater, C. Palleres, and R. C. Chao

Sunitinib was found effective in an open-label, two-stage, multicenter phase II study in patients with advanced non-small cell lung cancer (NSCLC) that had progressed following standard chemotherapy. Sunitinib is an oral tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor, platelet-derived growth factor receptor, KIT, FLT3, and RET on tumor cells, tumor neovasculature, and pericytes. Patients were eligible for inclusion in the study if they had confirmed diagnosis of NSCLC, Eastern Cooperative Oncology Group performance status score of 0–1, no recent gross hemoptysis, no brain metastases, adequate end-organ function, and if they were previously treated with 1–2 regimens of chemotherapy. Patients received sunitinib doses of 50 mg orally once per day for 4 weeks followed by 2 weeks of treatment, comprising one cycle. A total of 64 patients were enrolled (1 did not receive treatment) and continued on treatment until disease progression. Six patients (9.5%) experienced tumor shrinkage, considered a partial response and 26 patients (41%) had stable disease. In general, sunitinib was well-tolerated, with mild to moderate side effects, such as fatigue, nausea, shortness of breath, vomiting, anorexia, and diarrhea recorded. Serious side

effects included severe fatigue (19%), shortness of breath (13%), asthenia (9.5%), and nausea/vomiting (7%). Two patients died from bleeding in the lungs, and one died from bleeding in the brain. Based on the results, which lead author Dr. Mark A. Socinski said, “suggest that sunitinib may have a place in the treatment of lung cancer, alone or in combination with other agents,” the trial has been extended to explore a continuous dosing strategy of sunitinib administered orally at 37.5 mg/day.

7009 Adjuvant chemotherapy in elderly patients: An analysis of National Cancer Institute of Canada Clinical Trials Group and Intergroup BR.10

C. Pepe, B. Hasan, T. Winton, L. Seymour, J. Pater, R. Livingston, D. Johnson, J. Rigas, K. Ding, and F. Shepherd

Dr. Carmela Pepe and coauthors report that patients over 65 years of age with early-stage NSCLC can benefit from adjuvant chemotherapy after resection and face similar, acceptable levels of toxicities as compared to younger patients. Previous research showed that platinum-based chemotherapy given following surgery conferred significant benefits on patients with NSCLC in eliminating residual disease. It was unknown, however, whether elderly patients would benefit from such treatment as younger patients did. The researchers retrospectively evaluated data from the BR.10 trial, which compared the administration of cisplatin and vinorelbine with observation alone for patients with early-stage NSCLC. The outcomes of 327 young and 155 elderly (>65 years) patients matched for baseline prognostic factors (except histology and performance status) were compared. In the BR.10 trial, overall survival was significantly better with chemotherapy than observation in both age groups. In the present analysis, overall 5-year survival was found to be 66% in the chemotherapy group versus 46% in the observation group for elderly patients. Patients older than 75 years of age had significantly shorter survival than those age 66–74 years. Chemotherapy administration and toxicity were evaluated, and it was found that mean dose intensities of vinorelbine and cisplatin were 13.2 and 18.0 and 9.9 and 14.1 in the elderly and the young, respectively. The elderly also received significantly fewer doses of each drug. Fewer elderly patients completed treatment compared to the young. There were, however, no significant differences in toxicity, use of granulocyte colony-stimulating factor, or hospitalization between the age groups, but myalgias and mood alteration were more

common in the young group. Although the results clearly showed benefits of adjuvant chemotherapy in patients up to 75 years of age, further research is required in those older than 75 years because the sample size was small. “With these findings,” said Dr. Pepe, “we hope that physicians and patients can be assured that elderly patients will have a prolonged life and can be given this treatment without a fear of increased side effects because of their age.”

7520 A multicenter prospective randomized study testing non-inferiority of thalidomide 100 mg/day as compared with 400 mg/day in patients with refractory/relapsed multiple myeloma: Results of the final analysis of the IFM 01–02 study

I. Yakoub-Agha, C. Doyen, C. Hulin, G. Marit, L. Voillat, B. Grosbois, J. Harousseau, C. Duguet, R. Zerbib, T. Facon, and J. Mary

Due to the level of high-grade side effects seen in patients treated for relapsed or refractory multiple myeloma with high doses of thalidomide, research was undertaken to assess the efficacy and safety of lower doses of the drug. Despite the effectiveness of high-dose thalidomide (400 mg/day), which is the standard dose, numerous toxicities, such as somnolence, constipation, DVT, and peripheral neuropathy, cause many patients to discontinue treatment. In this multicenter, prospective study in France, 400 patients with multiple myeloma were randomized to receive doses of either 100 mg/day or 400 mg/day of thalidomide plus dexamethasone after 3 months of treatment in patients with stable disease or at any time in patients whose disease progressed. Patients also routinely received pamidronate. For enrollment, patients were required to have had at least one course of chemotherapy previously and 45% had received two or more courses; half the patients had undergone stem cell transplantation. The two patient groups were similar in patient characteristics and disease features, including prior therapy and chromosome 13 deletion. Patients who received the 100 mg/day dose of thalidomide received dexamethasone as per the protocol more frequently than those who received the high dose, but this difference did not affect the overall survival at 1 year. The rates of overall survival at 1 year were 73% in the high-dose group and 69% in the lower-dose group. The lower dose was tolerated better, with lower rates of somnolence (13% vs 33%), constipation (28% vs 40%), and peripheral neuropathy (20% vs 32%), but there was no difference between the groups in rates of

DVT. All patients who had a history of DVT were given oral anticoagulants, unlike in previous studies of thalidomide. Lead author Dr. Ibrahim Yakoub-Agha said, "This study shows that a low dose of thalidomide results in a very small decrease in survival, if any, as compared to the standard regimen, and has less severe side effects."

8505 Randomized trial of yoga in women with breast cancer undergoing radiation treatment

L. Cohen, K. Chandwani, B. Thornton, G. Perkins, E. Rivera, B. Arun, N. Raghuram, and H. Nagendra

A study evaluated the effects on quality of life of yoga for women undergoing treatment for breast cancer. Sixty-one women receiving radiation therapy were randomized to a yoga program or a waitlist control group. The yoga program entailed breathing and posture exercises and meditation, and patients attended biweekly classes for the

6 weeks of their treatment. Lead author Dr. Lorenzo Cohen said, "Because yoga deals with both mind and body, we hypothesized that cancer patients would benefit both physically and emotionally." The median age of patients was 52 years; 48% and 75% of patients had undergone breast-conserving surgery and had received chemotherapy, respectively. Patients were assessed for their well-being after the completion of radiation therapy. It was found that those who had participated in the yoga program had significantly better physical and social functioning as well as general health perceptions. Additionally, lower levels of fatigue and sleep disorders were reported in the patients who participated in yoga. There were, however, no differences reported between the groups in rates of depression and anxiety. A study is planned to include an active control group, in which patients who do not participate in yoga will take a class in general stretching exercises; investigators hope to determine whether the unique mind-body aspects of yoga or the emotional and social support of the class environment are responsible for the improved quality of life noted in the patients who took the yoga class.



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