

is associated with greater toxicity may be more desirable than long-term therapy with INH IL-2 that is less toxic but that can more severely impact patients' home life. For other patients, particularly those with a poorer overall performance status, the converse may be true. Thus, the IL-2 treatment modality should be tailored to the individual patient based on the patient's medical, psychological and emotional needs.

In summary, the results of the current analyses show that INH IL-2 and SYST IL-2 are comparably effective in promoting the survival of patients with mRCC. However, treatment with INH IL-2 is associated with considerably lower toxicity and fewer complications than SYST IL-2 treatment, thus providing a therapeutic option for otherwise untreatable patients, offering patients a relatively good quality of life (including the ability to maintain active social and professional roles), and requiring fewer co-medications. Nonetheless, one IL-2 treatment modality should not be considered to be superior to the other, but should be selected for a patient based on several patient-related considerations. Moreover, the two IL-2 treatment modalities need not be mutually exclusive. INH IL-2 treatment may be combined with SYST IL-2 therapy to potentially increase clinical benefit without augmenting toxicity.

Acknowledgement

We would like to acknowledge Susanne Wittneben and Barbara Kherad for their very valuable assistance with patient care and medical documentation.

References

- Angevin, E., Valteau-Couanet, D., Farace, F., Dietrich, P. Y., Lecesne, A., Triebel, F., Escudier, B. (1995) Phase I study of prolonged low-dose subcutaneous recombinant interleukin-2 (IL-2) in patients with advanced cancer. *J. Immunother. Emphasis Tumor Immunol.* **18**, 188-195.
- ASCO (1996) Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. *J. Clin. Oncol.* **14**, 671-679.
- Astoul, P., Bertault-Peres, P., Durand, A., Catalin, J., Vignal, F., Boutin, C. (1994) Pharmacokinetics of intrapleural recombinant interleukin 2 in immunotherapy for malignant pleural effusion. *Cancer* **73**, 308-313.
- Atzpodien, J., Kirchner, H. (1991) The out-patient use of recombinant human interleukin-2 and interferon alfa-2b in advanced malignancies. *Eur. J. Cancer* **27**, S88-S92.
- Atzpodien, J., Körfer, A., Evers, P., Franks, C. R., Knuver-Hopf, J., Lopez-Hanninen, E., Fischer, M., Mohr, H., Dallman, I., Hadam, M., et al. (1990a) Low-dose subcutaneous recombinant interleukin-2 in advanced human malignancy: a phase II outpatient study. *Mol. Biother.* **2**, 18-26.
- Atzpodien, J., Körfer, A., Franks, C. R., Poliwoda, H., Kirchner, H. (1990b) Home therapy with recombinant interleukin-2 and interferon- α 2b in advanced human malignancies. *Lancet* **335**, 1509-1512.
- Atzpodien, J., Kirchner, H., de Mulder, P., Bodenstein, H., Oliver, T., Palmer, P. A., Franks, C. R., Poliwoda, H. (1993a) Subcutaneous recombinant interleukin-2 and α -interferon in patients with advanced renal cell carcinoma: results of a multicenter phase II study. *Cancer Biother.* **8**, 289-300.
- Atzpodien, J., Kirchner, H., Hänninen, E. L., Korfer, A., Fener, M., Menzel, T., Deckert, M., Franzke, A., Jonas, U., Poliwoda, H. (1993b) European studies of interleukin-2 in metastatic renal cell carcinoma. *Sem. Oncol.* **20**, S22-S26.
- Atzpodien, J., Lopez Hänninen, E. L., Kirchner, H., Bodenstein, H., Pfreundschuh, M., Rebmann, U., Metzner, B., Illiger, H. J., Jakse, G., Niesel, T., et al. (1995) Multi-institutional home-therapy trial of recombinant interleukin-2 and interferon alfa-2 in progressive metastatic renal cell carcinoma. *J. Clin. Oncol.* **13**, 497-501.
- Bubeník, J. (1990) Local and regional immunotherapy of cancer with interleukin 2. *J. Cancer Res. Clin. Oncol.* **116**, 1-7.
- Bubeník, J., Perlmann, P., Indrová, M., Šímová, J., Jandlová, T., Neuwirt, J. (1983) Growth inhibition of an MC-induced mouse sarcoma by TCGF (IL-2)-containing preparations. *Cancer Immunol. Immunother.* **14**, 205-206.
- Buter, J., Sleijfer, D. T., van der Graaf, T. A., de Vries, E. G., Willemsse, P. H., Mulder, N. H., (1993) A progress report on the outpatient treatment of patients with advanced renal cell carcinoma using subcutaneous recombinant interleukin-2. *Sem. Oncol.* **20**, S16-S21.
- Buzio, C., De Palma, G., Passalacqua, R., Potenzoni, D., Ferrozzi, F., Cattabiani, M. A., Manenti, L., Borghetti, A. (1997) Effectiveness of very low doses of immunotherapy in advanced renal cell cancer. *Br. J. Cancer* **76**, 541-544.
- Elson, P. J., Witte, R. S., Trump, D. L. (1988) Prognostic factors for survival in patients with recurrent or metastatic renal-cell carcinoma. *Cancer Res.* **48**, 7310-7313.
- Enk, A. H., Nashan, D., Knop, J. (1997) Therapy of lung metastases of malignant melanomas with inhaled interleukin-2. *Der Hautarzt* **12**, 894-896. (in German)
- Escudier, B., Farace, F., Angevin, E., Charpentier, F., Nitenberg, G., Triebel, F., Hercend, T. (1994) Immunotherapy with interleukin-2 (IL-2) and lymphokine-activated natural killer cells: improvement of clinical responses in metastatic renal cell carcinoma patients previously treated with IL-2. *Eur. J. Cancer* **30**, 1078-1083.
- Figlin, R., Gitlitz, B., Franklin, J., Dorey, F., Moldawer, N., Rausch, J., deKernion, J., Beldegrun, A. (1997) Interleukin-2-based immunotherapy for the treatment of metastatic renal cell carcinoma: an analysis of 203 consecutively treated patients. *Cancer J. Sci. Am.* **3**, S92-S97.
- Foa, R., Guarinin, A., Gansbacher, B. (1992) IL-2 treatment for cancer: from biology to gene therapy. *Br. J. Cancer* **B**, 992-998.
- Gemlo, B. T., Palladino, M., Jaffe, H. S., Espevik, T. P., Rayner, A. A. (1988) Circulating cytokines in patients with metastatic cancer treated with recombinant interleukin 2 and lymphokine-activated killer cells. *Cancer Res.* **48**, 5864-5870.
- Heinzer, H., Mir, T. S., Huland, E., Huland, H. (1999) Subjective and objective prospective, long-term analysis of quality of life during inhaled interleukin-2 immunotherapy. *J. Clin. Oncol.* **17**, 3612-3620.
- Henriksson, R., Nilsson, S., Colleen, S., Wersall, P., Helsing, M., Zimmerman, R., Engman, K., (1998) Survival in renal cell carcinoma – a randomized evaluation of tamoxifen vs interleukin 2, α -interferon (leucocyte) and tamoxifen. *Br. J. Cancer* **77**, 1311-1317.
- Huland, E., Huland, H. (1989) Local continuous high-dose interleukin-2: a new therapeutic model for the treatment of advanced bladder carcinoma. *Cancer Res.* **49**, 5469-5474.

- Huland, E., Huland, H., Heinzer, H. (1992) Interleukin-2 by inhalation: local therapy for metastatic renal cell carcinoma. *J. Urol.* **147**, 344-348.
- Huland, E., Heinzer, H., Huland, H. (1994) Inhaled interleukin-2 in combination with low-dose systemic interleukin-2 and interferon alpha in patients with pulmonary metastatic renal-cell carcinoma: effectiveness and toxicity of mainly local treatment. *J. Cancer Res. Clin. Oncol.* **120**, 221-228.
- Huland, E., Heinzer, H., Mir, T. S., Huland, H. (1997) Inhalatory interleukin-2 therapy in pulmonary metastatic renal cell carcinoma: six years of experience. *Cancer J. Sci. Am.* **3**, S98-S105.
- Huland, E., Heinzer, H., Huland, H., Yung, R. (2000) Overview of interleukin-2 inhalation therapy. *Cancer J. Sci. Am.* **6**, S104-S112.
- Kolitz, J. E., Mertelsmann, R. (1991) The immunotherapy of human cancer with interleukin-2: present status and future directions. *Cancer Invest.* **9**, 529-542.
- Koretz, M. J., Lawson, D. H., York, M., Graham, S. D., Murray, D. R., Gillespie, T. M., Levitt, D., Sell, K. M. (1991) Randomized study of interleukin-2 (IL-2) alone vs IL-2 plus lymphokine-activated killer cells for treatment of melanoma and renal cell cancer. *Arch. Surg.* **126**, 898-903.
- Kruit, W. H. J., Goey, S. H., Lamers, C. H. J., Gratama, J. W., Visser, B., Schmitz, P. I., Eggermont, A. M., Bolhuis, R. L., Stoter, G. (1997) High-dose regimen of interleukin-2 and interferon-alpha in combination with lymphokine-activated killer cells in patients with metastatic renal cell cancer. *J. Immunother.* **20**, 312-320.
- Law, T. M., Motzer, R., Mazumdar, M., Sell, K. W., Walther, P. J., O Connell, M., Khan, A., Vlamis, V., Vogelzang, N. J., Bajorin, D. F. (1995) Phase III randomized trial of interleukin-2 with or without lymphokine-activated killer cells in the treatment of patients with advanced renal cell carcinoma. *Cancer* **76**, 824-832.
- Lee, R. E., Lotze, M. T., Skibber, J. M., Tucker, E., Bonow, R. O., Ognibene, F. P., Carrasquillo, J. A., Shelhamer, J. H., Parrillo, J. E., Rosenberg, S. A. (1989) Cardiorespiratory effects of immunotherapy with interleukin-2. *J. Clin. Oncol.* **7**, 7-20.
- Lissoni, P., Barni, S., Ardizzosa, A., Crispino, S., Paolorossi, F., Archili, C., Vaghi, M., Tancini, G. (1992) Second line therapy with low-dose subcutaneous interleukin-2 alone in advanced renal cell cancer patients resistant to interferon-alpha. *Eur. J. Cancer* **28**, 92-96.
- Lissoni, P., Barni, S., Ardizzosa, A., Andres, M., Scardino, E., Cardellini, P., Della Bitta, R., Tancini, G. (1993) A randomized study of low-dose interleukin-2 subcutaneous immunotherapy versus interleukin-2 plus interferon-alpha as first line therapy for metastatic renal cell carcinoma. *Tumori* **79**, 397-400.
- Lissoni, P., Barni, S., Ardizzosa, A., Crispino, S., Paolorossi, F., Andres, M., Scardino, E., Tancini, G. (1994) Prognostic factors of the clinical response to subcutaneous immunotherapy with interleukin-2 alone in patients with metastatic renal cell carcinoma. *Oncology* **51**, 59-62.
- Lissoni, P., Barni, S., Ardizzosa, A., Frigerio, F., Paolorossi, F., Cazzaniga, M., Tancini, G., Rocco, F., Aapro, M. (1995) Clinical efficacy of cancer subcutaneous immunotherapy with interleukin-2 in relation to the pretreatment levels of tumor growth factor insulin-like growth factor-1. *Tumori* **81**, 261-264.
- Lorenz, J., Wilhelm, K., Kessler, M., Peschel, C., Schwulera, U., Lissner, R., Struff, W. G., Huland, E., Huber, C., Aulitzky, W. E. (1996) Phase I trial of inhaled natural interleukin 2 for treatment of pulmonary malignancy: toxicity, pharmacokinetics, and biological effects. *Clin. Cancer Res.* **2**, 1115-1122.
- Marincola, F., White, D. E., Wise, A. P., Rosenberg, S. A. (1995) Combination therapy with interferon alfa-2a and interleukin-2 for the treatment of metastatic cancer. *J. Clin. Oncol.* **13**, 1110-1112.
- Negrier, A., Escudier, B., Lasset, C., Douillard, J. Y., Savary, J., Chevreau, C., Ravaud, A., Mercatello, A., Peny, J., Mousseau, M., Philip, T., Tursz, T. (1998) Recombinant human interleukin-2, recombinant human interferon alpha-2a, or both in metastatic renal cell carcinoma. *N. Engl. J. Med.* **338**, 1272-1278.
- Palmer, P. A., Atzpodien, J., Philip, T., Negrier, S., Kirchner, H. (1993) A comparison of 2 modes of administration of recombinant interleukin-2: continuous intravenous infusion alone versus subcutaneous administration plus interferon alpha in patients with advanced renal cell carcinoma. *Cancer Biother.* **8**, 123-136.
- Petzoldt, B., Prietl, G., Kupka, M., Köhler, S., Krebs, D., Wagner, U. (1999) Combination therapy of pulmonary metastasised gynaecological cancer with inhalative interleukin-2: results of a feasibility study. *Geburtsh. Frauenheilk.* **59**, 157-162. (in German)
- Ravaud, A., Négrier, S., Cany, L., Merrouche, Y., Le Guillou, M., Blay, J. Y., Clavel, M., Gaston, R., Oskam, R., Philip, T. (1994) Subcutaneous low-dose recombinant interleukin 2 and alpha-interferon in patients with metastatic renal cell carcinoma. *Br. J. Cancer* **69**, 1111-1114.
- Roigas, J. (1999) Inhalation of interleukin-2 as second-line treatment: Charite experience. *Anticancer Res.* **19**, 2010-2011 (Abstract).
- Slejfer, D. T., Janssen, R. A. J., Buter, J., de Vries, E. G., Willemse, P. H., Mulder, N. H. (1992) Phase II study of subcutaneous interleukin-2 in unselected patients with advanced renal cell cancer on an outpatient basis. *J. Clin. Oncol.* **10**, 1119-1123.
- Steis, R. G., Urba, W. J., VanderMolen, L. A., Bookman, M. A., Smith, J. W. 2d, Clark, J. W., Miller, R. L., Crum, E. D., Beckner, S. K., McKnight, J. E., et al. (1990) Intraperitoneal lymphokine-activated killer-cell and interleukin-2 therapy for malignancies limited to the peritoneal cavity. *J. Clin. Oncol.* **8**, 1618-1629.
- Tourani, J. M., Lucas, V., Mayeur, D., Dufour, B., DiPalma, M., Boaziz, C., Grise, P., Varette, C., Pavlovitch, J. M., Pujade-Lauraine, E., Larregain, D., Ecstein, E., Untereiner, M., Vuillemin, E., Merran, S., Andrieu, J. M. (1996) Subcutaneous recombinant interleukin-2 (rIL-2) in out-patients with metastatic renal cell carcinoma. *Ann. Oncol.* **7**, 525-528.
- Vuoristo, M., Jantunen, I., Pyrhönen, S., Muhonen, T., Kellokumpu-Lehtinen, P. (1994) A combination of subcutaneous recombinant interleukin-2 and recombinant interferon- α in the treatment of advanced renal cell carcinoma or melanoma. *Eur. J. Cancer* **30**, 530-532.
- Whitehead, R. P., Ward, D., Hemingway, L., Hemstreet, G. P., 3rd, Bradlez, E., Konrad, M. (1990) Subcutaneous recombinant interleukin 2 in a dose-escalating regimen in patients with metastatic renal cell adenocarcinoma. *Cancer Res.* **50**, 6708-6715.