Tumori, 95: 129-131, 2009

LETTERS TO THE EDITOR

Long-lasting remission of a relapsed large cell non-Hodgkin's lymphoma by Y90 ibritumomab tiuxetan as salvage therapy

Alessio Pio Perrotti[1], Pasquale Niscola[1], Sergio Boemi[2], Laura Scaramucci[1], Teresa Dentamaro[1], Massimiliano Palombi[1], Micaela Ales[1], Luca Cupelli[1], Andrea Tendas[1], Daniela Piccioni[1], Marco Giovannini[1], Virginia Naso[3], Maurizio Martelli[3], and Paolo de Fabritiis[1]

[1]Hematology Division, Tor Vergata University, Sant'Eugenio Hospital, Rome; [2]Division of Nuclear Medicine, Sant'Eugenio Hospital, Rome; [3]Department of Cellular Biotechnology and Hematology, Sapienza University, Rome, Italy

To the Editor: Radioimmunotherapy by Y90 ibritumomab tiuxetan, which targets the CD20 antigen, in B-cell lymphoma has clearly demonstrated efficacy and tolerability with high response rates and long durability of remission in relapsed and refractory disease[1,2]. Patients benefiting from this therapy include those unsuitable for myeloablative treatments and autologous stem cell transplantation[3,4], as illustrated by the case observed by us and reported here.

A 68-year-old woman came to our attention in January 2001 because of an enlarged left axillary lymph node. Her past medical history was unremarkable and she had no systemic symptoms. The node was removed and histological examination revealed diffuse large B-cell lymphoma (DLBCL). A comprehensive clinical and radiological workup was done. Computed tomography (CT) of the chest, abdomen and pelvis showed left axillary and subdiaphragmatic lymph nodes. A bone marrow trephine biopsy revealed no pathological findings, so the patient was considered to have clinical stage IIIA disease.

According to the International Prognostic Index (IPI) score, our patient belonged to the intermediate to high risk group. She was given combination chemotherapy consisting of prednisone, doxorubicin, etoposide, cyclophosphamide, vincristine and bleomycin (P-VABEC regimen)[5], by which she achieved CT-confirmed complete remission in June 2001.

Six months later she presented with an enlarged node in the right axilla; surgical excision was performed and relapse of DLBCL demonstrated. Comprehensive reevaluation including whole-body CT and another trephine biopsy was done. The patient was diagnosed as having clinical stage IIIA DLBCL with the same IPI score as at disease onset. She refused high-dose chemotherapy and autologous stem cell transplantation. She was therefore offered alternative salvage therapy, for which she was properly informed and gave her written consent.

Starting from December 2001, she received rituximab (250 mg/m^2) followed 6 days later by the same dose of rituximab conjugated with Y90 ibritumomab tiuxetan 1182 MBq (0.4 mCi/kg). Hematological toxicity was unremarkable (grade II WHO). She developed severe bronchopneumonia (grade III WHO) requiring hospitalization and intensive medical care. After the patient's recovery, restaging studies documented complete remission, which was stably maintained for 85 months, as confirmed by a recently performed total-body positron-emission tomography (PET)/CT scan.

In the presented case, the patient received a single treatment of Y90 ibritumomab tiuxetan, resulting in long-lasting PET/CT-confirmed complete response for more than 6 years. This finding is rather unusual in relapsed DLBCL patients, which generally showed poor responses to this agent when administered alone[3].

Although it should not be concluded that Y90 ibritumomab tiuxetan may have a curative role in advanced DLBCL, our case outlines the possibility of a rapid and long-lasting response even in this poor-prognosis group of patients. In addition, the short time required for delivering the treatment plan and the low and manageable toxicity makes this agent an ideal tool in elderly patients with DLBCL.

References

1. Wiseman GA, Kornmehl E, Leigh B, Erwin WD, Podoloff DA, Spies S, Sparks RB, Stabin MG, Witzig T, White CA: Radiation dosimetry results and safety correlations from 90-Yibritumomab tiuxetan radioimmunotherapy for relapsed or refractory non-Hodgkin's lymphoma: combined data from 4 clinical trials. J Nucl Med, 44: 465-474, 2003.
2. Davies AJ: Radioimmunotherapy for B-cell lymphoma: Y90 ibritumomab tiuxetan and I (131) tositumomab. Oncogene, 26: 3614-3628, 2007.
3. Morschhauser F, Illidge T, Huglo D, Martinelli G, Paganelli G, Zinzani PL, Rule S, Liberati AM, Milpied N, Hess G, Stein H, Kalmus J, Marcus R: Efficacy and safety of yttrium-90 ibritumomab tiuxetan in patients with relapsed or refractory diffuse large B-cell lymphoma not appropriate for autologous stem-cell transplantation. Blood, 110: 54-58, 2007.
4. Witzig TE, Molina A, Gordon LI, Emmanouilides C, Schilder RJ, Flinn IW, Darif M, Macklis R, Vo K, Wiseman GA: Long-term responses in patients with recurring or refractory B-cell non- Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan. Cancer, 109: 1804-1810, 2007.

Correspondence to: Alessio Perrotti, Hematology Unit, S. Eugenio Hospital, Piazzale dell'Umanesimo 10, 00144 Rome, Italy. Tel +39-06-51002105; fax +39-06-51002333; e-mail alessioperrotti@gmail.com

5. Martelli M, Guglielmi C, Coluzzi S, Avvisati G, Amadori S, Giovannini M, Torromeo C, Mandelli F: P-VABEC: a prospective study of a new weekly chemotherapy regimen for elderly aggressive non-Hodgkin's lymphoma. J Clin Oncol, 11: 2362-2369, 1993.

Metronomic chemotherapy in elderly patients: do risks exceed benefits in some patients?

To the Editor: In Tumori 2007[1], a case report was recently published about the treatment with metronomic chemotherapy of an 84-year-old woman with metastatic breast cancer. The authors question if "risks (do not) exceed benefits in some patients?" even using such a treatment, which is known to be very well tolerated for the average patient. The described patient, defined as "frail", died after one week including three days of treatment with cyclophosphamide, 50 mg per day, and methotrexate, 5 mg given during a single day. The early onset of grade 4 neutropenia and thombocytopenia, severe diarrhea and renal failure led to what was interpreted to be a cytotoxic-related death (on day 7). Guidelines on who should or should not be treated among elderly patients are a main topic of the Discussion[2].

The authors also discussed the use of this kind of chemotherapy in an adjuvant setting[3] in order to alert about the potential risks of this treatment. Three important issues need though to be emphasized. First, the authors cited the CASA adjuvant trial in which such treatment is a randomized option. CASA was conceived for frail elderly patients whose conditions led their physicians to exclude standard adjuvant chemotherapy, yet to justify the use of adjuvant regimens suitable for the vulnerable but not prohibitive, as in the case of the reported patient. The described patient was probably better treated by proper supportive care alone and without cytotoxic drugs. In fact, the inclusion criteria for the CASA trial, besides the main feature of having endocrine non-responsive tumors, include intact organ function at the time of randomization, and require adequate bone marrow, renal and hepatic functions: WBC ≥ 3.0 x 10^9/L, granulocyte count ≥ 1,500 x 10^9/L, platelet count ≥ 100 x 10^9/L, serum creatinine <120 μmol/L (< 1.35 mg/dl), calculated creatinine clearance at least 50 mL/min, serum bilirubin within normal/reference range, AST/ALT within 1.5 x the upper normal limit, as well as adequate cardiovascular function defined as: LVEF ≥ 50% by echocardiography, radionuclide ventriculography or multigated angiography (MUGA), no ECG evidence of acute ischemia or previous myocardial infarction within the past 6 months, no New York Heart Association (NYHA) class III or IV congestive heart failure, no evidence of medically relevant conduction system abnormalities, which in the opinion of the investigator would preclude trial entry.

The second point relates to what the authors defined as "mildly" altered liver function tests of the patient (who had liver metastases). Both cyclophosphamide and methotrexate undergo liver metabolization, as the authors finally recognize. There was an abnormal and probably also genetically determined increased sensitivity to toxicity of these agents, due to enzymatic isoforms resulting in enhanced activation of cellular utilization of the drugs. As the authors pointed out, the patient's compliance using oral drugs is also particularly important. This aspect is increasingly important due to availability of new oral agents which require even more attention to compliance, requiring also specific studies of bioavailability[4] and of pharmacogenetics.

The third point relates to methodological issues and to the attention given to " burdens and benefits" within the studies conducted by the International Breast Cancer Study Group in general and for the elderly in particular[5]. This case is exemplar for the validity of the concept that treating an elderly patient is complex and requires a fine evaluation of variables to discriminate between those who need and might benefit from cancer treatment from those who might enjoy the effects of supportive care without a specific addition of cancer therapy. Often this is a fair question for patients at any age and the elderly deserve no less.

Diana Crivellari[1], Marco Colleoni[2], Silvia Dellapasqua[2], and Aron Goldhirsch[2]
[1]Department of Medical Oncology C, Centro di Riferimento Oncologico, Aviano; [2]Department of Medicine, European Institute of Oncology, Milan, Italy

References

1. Arnoldi E, Dieli M, Mangia M, Labianca R: Metronomic chemotherapy in elderly patients: do risks exceed benefits in some patients? Tumori, 93: 647, 2007.
2. Balducci L, Yates J: General guidelines for the management of older patients with cancer. Oncology, 14(11A): 221-227, 2000.
3. Crivellari D, Aapro M, Leonard R, von Minckwitz G, Brain E, Goldhirsch A, Veronesi A, Muss H: Breast cancer in the elderly. J Clin Oncol, 25: 1882-1890, 2007.
4. Findlay M, Von Minckwitz G, Wardley A: Effective oral chemotherapy for breast cancer: pillars of strength. Ann Oncol, 19: 212-222, 2008.
5. Crivellari D, Bonetti M, Castiglione-Gertsch M, Gelber RD, Rudenstam CM, Thürlimann B, Price KN, Coates AS, Hürny C, Bernhard J, Lindtner J, Collins J, Senn HJ, Cavalli F, Forbes J, Gudgeon A, Simoncini E, Cortes-Funes H, Veronesi A, Fey M, Goldhirsch A: Burdens and benefits of adjuvant cyclophosphamide, methotrexate, fluorouracil and tamoxifen for elderly patients with breast cancer: The International Breast Cancer Study Group Trial VII. J Clin Oncol, 18: 1412-1422, 2000.

IN REPLY: As regards the observations about our case report (Tumori, 93, 2007) made by Crivellari *et al.*, we think that their comments are widely agreeable, particularly as regards the invitation to keep a careful eye on every chemotherapy, especially in the elderly.

The provoking title of our work had the purpose to underline the need for particular attention in the care of elderly cancer patients. It is known that the side effects of a certain drug are not always predictable, since every patient has a peculiar genetic background, which can interfere with the susceptibility to treatments. In this case, the low dosage of the prescribed drug (if we assume that is was correctly ingested) cannot explain the severe toxicity observed.

Even if oral administration is considered the simplest and safest way to deliver oncological treatments, our experience suggests that it may not always be true and sometimes there is no certainty about the dosage actually administered at home despite a clear medical prescription.

Ermenegildo Arnoldi[1], Roberto Labianca[1], Maria Dieli[2], and Marina Mangia[2]
[1]Department of Medical Oncology, [2]Department of Internal Medicine, Ospedali Riuniti, Bergamo, Italy