THE QUALITY OF LIFE IMPROVEMENT IN PATIENTS ADMINISTERED CYTOTOXIC DRUGS AS THE RESULT OF NEW SUPPORTIVE METHODS OF THERAPY APPLICATION.

C. RAMLAU, L. RUMIANOWSKI, M. LITWINIUK, P. TOMCZAK, R. RAMLAU*.

Chair of Oncology Faculty of Medicine K. Marcinkowski University School of Medicine, Poznań, Poland.* Oncology Department, Regional Lung Diseases Hospital, Poznań, Poland.

KEY WORDS :cytotoxic therapy, quality of life, supportive treatment Nausea and vomiting due to aggressive chemotherapy are additional burden for cancer patients.

In recent years new anti-emetic agents have been developed.These drugs greatly reduce or eliminate chemotherapy -related nausea and vomiting.

Introduction of new drugs as G-CSF (Neupogen), rHuGM-CSF (Leucomax) and Eprex (rHu-EPO) gave the possibility to prevent serious chemotherapy side-effects like leucopenia and anaemia.

Supportive treatment in cancer patients enormous influence the quality of life and reduce therapy- related anxiety.

In our Oncological Clinic this supportive treatment has been used for 3 years allowing more aggresive therapy.

PREFACE

In 1984 Till, McNeil and Bush defined *quality of life* as a total idea including psychical and social activity, physical action and profitable aspects of being in a good frame of mind as well as negative ones coused by disease and invalidity [Dawid M.D., 1993].

The quality of life is estimated subjectively and only the patient can compare his present condition with the one he would like to have and which would be a normal one for him [Dawid M.D., 1993]. So he patient's opinion is the most important and should be taken into account every time when it is possible.

When the patient cannot answer the question about his quality of life then the opinions of people who look after him could be considered but still one should be careful because considerable disagreements in evaluations of quality of life among opinion of doctors, relatives and patients have been noticed.

The quality of life depends on patient's physical and psychical condition, so all methods of adjuvant therapy are very valuable and should be videly used in oncological clinic.

Recently a new group of antiemetic drugs, 5-HT 3- receptor antagonists [Aapro, 1993; Ramlau et al, 1993; Kytril, 1993] have been applied in clinic. Those agents help eliminate nausea and vomiting to a great extent. Chemotherapy induced nausea and vomiting were the reason for refusing futher therapy by some patients although it could be curative. As a consequence of aggravation of cancer patient'shealth, the quality of life worsened. At the same time a new possibility of preventing serious chemotherapy related side-effects like granulocytopenia and anaemia appeared. This was connected with administration of haematopoietic growth factors such as Neupogen (G-CSF), Leucomax (rHuGM-CSF) and Eprex (rHu-EPO) [Neupogen, Leucomax, 1993; Eprex].

Application of a new supportive methods in patients receiving cytotoxic drugs has caused a noticeable improvement of therapy conditions and treatment-related anxiety. Consequently the quality of life of our patients has improved.

NAUSEA AND VOMITING

Development of chemotherapy and new chemotherapy regimens application reduces tumour mass and improves response rates, therefore it leads to extention of patients' survival time and improvement of quality of their lives. However, cytotoxic agents are also toxic and induce very unpleasant side-effects like nausea and vomiting .Those drawbacks make therapy unbearable. Moreover, nausea and vomiting were the main reason for refusing chemotherapy by some patients although it could be curative.Unpleasant and harmful side-effects must be prevented or reduced in order to make the treatment acceptable by the patients and the medical staff.

Additionally, nausea and vomiting can bring weakness and exhaustion which interfere with

everyday patient's activity. Another consequence of side-effects mentioned above is lasting anorexia leading to chronic malnutrition and loss of liquids which needs intravenous supplement.

It is considered that there are two anatomically and functionally different areas which are responsible for regulation of vomiting reflex .They are located in medulla oblongata [Ramlau et al, 1993].

First of them, *Chemoreceptor trigger zone*, is situated on both sides of the bottom of fourth cerebral ventricle. *Chemoreceptor trigger zone* is in contact with blood and cerebrospinal fluid abounding with neurotransmitters. This area adheres to the second one-*Vomiting centre.* It is essential for vomiting reflex. *Vomiting centre* is located close to *Respiratory centre* and *Saliva secretion regulating centre.* Those centres coordinate secretion of mucous glands with involuntary contractions of diaphragm, thoracic and abdominal muscles, which are due to vomiting effect.

At first cytotoxic drugs affect *Chemoreceptor trigger zone.* Then impulses reach *Vomiting centre.* The impulses can also go by way of the throat and the upper part of gastrointestinal tract through afferent fibres of vagus nerve and symphatetic system.Certain parts of cerebral cortex may stimulate *Vomiting centre*, too.

NEW ANTI-EMETIC DRUGS

Zofran (ondansetron)-5-HT 3 receptor antagonist [3] is very effective in controlling chemotherapy and radiotherapy- related nausea and vomiting, much more effective than metoclopramide. From April till May 1991 in Chemotherapy Ward, Oncological Clinic of K.Marcinkowski University School of Medicine in Poznań 10 patients treated with chemotherapy (5 with cisplatin and 5 with other drugs) were administered Zofran (from *Glaxo*).Cisplatin-treated patients were given 8 mg of Zofran intravenously before cisplatin, the second and the third ampoule (a 8 mg) every 8 hours. Next day and the following ones Zofran was given in tablets in case of emesis continued.

The other 5 patients were administered 8 mg of Zofran intravenously before cytotoxic drugs and next 8 mg in tablets every 8 hours.The results were estimated in a 5- grade evaluation scale in comparison with previously aplied anti-emetic drugs (the grades were: very good, good , average , poor , no effective). Very good results were obtained by 80 % of patients and good ones by 20 %. In three cases intensive vomiting- resistant to previous antiemetic drugs-stopped. Up till now many patients have been given Zofran many times. The overall results are similar to the mentioned above.

Navoban (tropisetron) is another antagonist of serotonin-receptor [1].It has been used in Oncological Clinic in Poznań for 3 years. It is a product of *Sandoz* .

Doing research together with Radiotherapy Clinic of Oncology Institute in Gliwice we had a chance to prove a high anti-emetic efficacy of Navoban. In randomised controlled clinical trial quality of Navoban was compared with efficacy of traditional anti-emetic agents i.e. dexamethasone and metoclopramide.

Good results (minimal nausea and no more than 2 episodes of vomiting) were obtained in 89 % of patients receiving Navoban and in 38 % of patients receiving dexamethasone and metoclopramide. In cisplatin-treated patients good results were obtained in 86 % of them, while for other cytotoxic drugs in 95 %.

Very good results (no nausea and vomiting) were noted in 69 % of Navoban-and only in 17 % of dexamethasone and metoclopramide-administered patients.

Kytril (granisetron) [5] is the third of anti-emetic drugs (serotonin-receptor antagonist). According to the producer *Smith Kline Beecham* Kytril is the best anti-emetic agent of 5-HT 3-receptor antagonists.

In August and September 1994 antiemetic efficacy of Kytril was evaluated in our Clinic. 31 patients were administered 3 mg of Kytril intraveniously directly before cytotoxic drugs as cisplatin, cyclophosphamide, epirubicin, dacarbazine. On the first day of treatment nausea and vomiting appeared in 30 % of the patients. Than, on the following days in only 10 % of them.

Now anti-emetic quality of granisetron combined with corticosteroids is under randomised controlled study in our Clinic.

GROWTH FACTORS AND IMPORTANCE OF THEIR INTRODUCTION INTO ONCOLOGY CLINIC

Application of Neupogen (filgrastim, G-CSF) [Neupogen], a product of *Roche,* as a haematopoetic growth factor was initiated in the years 1991-1993.

It is the first of various growth factors, which influences number of white cells (neutrophils). Thus Neupogen is applied in prophylaxis of infections caused by bone marrow supression as a consequence of chemotherapy.

The authors (J.A.Green) using Neupogen on a large scale tend to administrate cytotoxic drugs in maximum dose and in a wright time.One should also consider the economic side of employing growth factors in reducing costs of treatment and first of all in improving the

quality of patient life. Application of high doses of cytotoxic drugs with Neupogen may give some good results in treatment of common doses-resistant tumours. Intravenous or subcutaneous G-CSF injections (0,5 MU / kg / 24 hrs) on the following day after chemotherapy are recommended.

According to W. Hiddeman and co-workers employing filgrastim in acute myeloid leucaemia reduced mortality from 39 % to 14 %. Neupogen has been succesfully administered several times in our Clinic. Leucomax (rHu GM-CSF -molgramostim) [Leucomax, 1993], a product of *Sandoz* and *Schering-Plough* has been shown as another useful haematopoietic growth factor in our Clinic. It is a water soluble, 127 amino acids-containing recombinant human granulocyte -macrophage colony stimulating factor. Molgramostin is produced by a strain of Escherichia coli bearing a genetically engineered plasmid which contains a human GM-CSF gene.Leucomax is indicated :

- in patients receiving myelosuppressive therapy (cancer chemotherapy) to reduce the severity of neutropenia, thereby reducing the risk of infection and allowing better adherence to the chemotherapeutic regimen;
- in patients presenting with other bone marrow failure states (myelodysplastic syndromes / aplastic anaemia) to reduce the risk of infection originating from leucopenia;
- in patients undergoing autologous or syngeneic bone marrow transplantation to accelerate myeloid recovery; - in patients with leucopenia associated with infections (incl. HIV)
- in patients with AIDS-related cytomegalovirus (CMV) retinitis.

Leucomax dosing regimens vary according to the indication for therapy (in cancer chemotherapy 5 to10 micrograms / kg per day of molgramostim administered subcutaneously Treatment should be initiated 24 hours after the last dose of chemotherapy and continued for 7 to 10 days.

Eprex (r-Hu EPO-erythropoietin) made by *Janssen-Cilag* can improve the quality of life of our patients by increasing of haemoglobin level and thus relieves anaemia- connected symptoms (like weakness).Well tollerated Eprex may reduce the need for transfusion, therefore eliminate risks associated with blood transfusion. Eprex has been administered cancer patients (in ovary- cancer especially) since december 1993. Subcutaneous injections of Eprex in dose of 150 to 300 IU / kg, 3 times a week, are recommended.

The only disadvantage of those new drugs, especially the growth factors, may be their very high price.

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