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RNA Fragments (RLB) and Tolerance of Cytostatic Treatments in Hematology: A Preliminary Study about Two Non-Hodgkin Malignant Lymphoma Cases

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Zusammenfassung

Die Untersuchungen wurden mit kurzkettigen RNS-Fragmenten (RLB) durchgeführt, um festzustellen, ob diese Chemotherapie-induzierte Neutropenie und Thrombopenie verhindern oder verringern können sowie die Nebenwirkungen abzuschätzen. Wir studierten beide ersten Patienten im Alter von 65 und 77 Jahren mit Non-Hodgkin-Lymphomen. Die kurzkettigen RNS, die jeden zweiten Tag sublingual verabreicht wurden, erscheinen bei dieser Indikation wirksam zu sein. Neutrophile und Thrombozyten werden signifikant erhöht. Außerdem werden RNS-Fragmente gut vertragen, und es wurden keine Nebenwirkungen beobachtet. Die Chemotherapie-Protokolle konnten ohne Unterbrechung der Behandlung fortgesetzt werden, und es gab keine Notwendigkeit, die Zytostatika-Dosis zu reduzieren.

Schlüsselwörter

Chemotherapie, Krebs, Antimitotika, RNS-Fragmente, Leukozyten, Thrombozyten, maligne Non-Hodgkin-Lymphome, medulläre Aplasie.

Summary

Assays were carried out with short-chain RNA fragments (RLB) in order to determine whether they can prevent or decrease chemotherapy-induced neutropenia and thrombopenia, as well as to evaluate side effects. We studied both first patients, 65 and 77 years old with non-Hodgkin lymphoma. The short-chain RNAs, administered by sublingual way every second day, appear useful in this indication. Neutrophils and platelets are significantly increased. In addition, tolerance of the RNA fragments is good and no side effect is observed. Chemotherapy protocols could be followed without treatment interruptions and there was no need to decrease cytostatic agent doses.

Keywords

Chemotherapy, cancer, antimitotics, RNA fragments, leukocytes, platelets, non-Hodgkin malignant lymphoma, medullary aplasia.

Introductions

Chemotherapy-treated cancer patients frequently develop neutropenia and thrombopenia, which often lead to bacterial, and, secondarily, to fungal infections, as well as to coagulation disorders. Patients who develop fever, neutropenia and thrombopenia have to be hospitalized and must undergo intensive intravenous (i.v.) antibiotic therapy [1]. Mortality because of secondary infections may reach 30% of the total number of deaths [1], and even more when patients are aged [2].

Treatments based on the use of growth factors have been proposed [2, 3], following studies carried out on patients suffering from acute myeloblastic leukemia [4, 5], from lymphomas [6], jointly with bone marrow transplants [7] and from various syndromes involving neutropenia, such as acquired immunodeficiency syndrome (AIDS) [8]. These treatments have dose-dependent side effects, and, in addition, induce myalgia, arthralgia, hair loss, as well as oedema and pericardial and pleural extravasation. Potential toxicity is assumed for long-term treatments [3]. Even more disturbing is a study on the stimulating effect these growth factors exert on solid tumors [9]. Short-chain RNA fragments (RLB) were assayed in vitro and in vivo with the aim of correcting chemotherapy-induced loss of neutrophils and platelets [10]. Experimentally, these molecules were shown to protect rabbits from neutropenia induced by cytostatic agents such as cyclophosphamide [11, 12] and from the platelet-depleting effects of daunorubicin [13]. Studies later carried out on human patients confirmed this activity [10]. The objective of our present study is to demonstrate the effects of RLB on 2 patients, 65 and 77 years old, suffering from non-Hodgkin malignant lymphoma. One of them had undergone several chemotherapeutic treatments before RLB administration. For the other one, these molecules were given following the initial treatment.

Methods

The patients studied were chosen for the important therapeutic problems they presented (old-age, malignant lymphoma, bad tolerance of their first chemotherapy treatment (biological rank IV and clinical rank I and II according to the OMS classification: tab. 1)

Case 1, 66 years old, had been medically followed for two years for a non-Hodgkin lymphoma, of the centroblastic centrocytic histological type, with an important tumor part and an isolated abdominal localization (Stage I). This (female) patient had undergone uninterrupted chemotherapy since 11 August 1988, first of the CHOP-BLEOMYCIN type, then of the CHOP type.

Abbreviations: RLB: specific RNA fragments [10]; RNA: ribonucleic acid; AIDS: Acquired immunodeficiency syndrome.

Tab. 1: OMS biological and clinical tolerance rank for chemotherapy.

Rank	O	I	II	III	IV
Biological					
Hemoglobin (g/L)	>11	9.5-10.9	8-9.4	6.5-7.9	<6.5
Leukocytes ($.10^3/mm^3$)	>4	3-3.9	2-2.9	1-1.9	<1
Neutrophils ($.10^3/mm^3$)	>2	1.5-1.9	1-1.4	0.5-0.9	<0.5
Platelets ($.10^3/mm^3$)	>100	75-99	50-74	25-49	<25
Clinical					
Fever (°)	Usual	<38	38-40	>40	>40
According to Infection	No	Minor	Moderate	Major	Hypotension Schock

Tab. 2: Biological and clinical rank of chemotherapy tolerance for subject 1 and 2.

	Cure 1		Cure 2		Cure 3		Cure 4	
Subject	1	2	1	2	1	2	1	2
Biological Rank	IV	IV	IV	III	IV	III	IV	–
Clinical Rank	II	I	0	0	0	0	0	–
Cure Apart in days	57	35	49	28	50	–	–	–
RLB	–	–	+	+	+	+	+	

Clinical remission was obtained with the third treatment. Then, a maintenance chemotherapy is followed with the COP type, without vincristine. A ganglionnary type relapse occurs in april 1990. A chemotherapy of the CH2OP type without vincristine, with seven days apart treatments (tab. 1), is done (four treatments are envisaged). The first treatment was followed by a long neutropenia period, with 38.5° fever, grippal syndrome, general state deterioration. The patient had to be hospitalized, with antibiotic therapy. The following cure has been one-week deferred. RLB (20 mg of lyophilizate) is administered every other day, two days before the second cure. Under RLB, the three following treatments were done at the same posology with a seven week interval.

Case 2, 77 years old, was taken charge of at the beginning of 1990 for a Stage IV cervical and thyroid non-Hodgkin malignant lymphoma. Two histological types were found in this (female) patient. Results of thyroid sample morbid anatomy indicated a centroblastic, large cell non-Hodgkin lymphoma, while those of bone biopsy favored a small cell, medullary non-Hodgkin malignant lymphoma. Therapeutic strategy consisted of a CHOP-BLEOMYCIN type polychemotherapy with the usual dose of anthracyclin, one treatment per month. A poorly tolerated aplasia and slow neutrophils and platelets augmentation have followed the first treatment. Both last treatments were done with RLB (20 mg of lyophilizate) administered every other day, one day before the second treatment.

Results and Discussion

Clinical results are presented in tab. 2 and biological results in fig. 1 and 2 and tab. 2.

RLB treatment is very well tolerated, and, until now, has induced no side effects and has in no way incommoded patients.

In intensive chemotherapy, abundant toxic effects are observed. Doxorubicine posology must be reduced, and the administered on anticipated doxorubicin posology ratio which may give the remission, become inferior to one.

Case 1: RLB administration allowed reintroduction of doxorubicin and chemotherapy protocols could be regularly applied. All treatments had a biological rank IV. The neutrophils and platelets re-increased rapidly and, for the third treatment without platelets decrease. The first treatment had a clinical rank II, and the others a rank 0 with perfect tolerance and without hospitalization. The treatments were all done at the same posology and seven weeks apart. The administered on anticipated doxorubicin posology ratio is equal to 1. This point is important, because remission depends on the total dose of cytostatic agents which may be given to patients. The patient is in remission from his last relapse.

Case 2: The first treatment had a biological rank IV and the others III, but without platelets decrease, aplasia and the re-increase of neutrophils is rapid. The last two treatments have a clinical rank 0, without fever and infection. The administered on anticipated doxorubicin posology ratio is equal to 1. The patient is in remission.

Conclusion

RLB is very simple to administer (with better compliance, using this posology), without constraint for patients. It gives better biological and clinical tolerance of chemotherapy usually with aplasia, reduces the morbidity and hospital stays.

Its action is clinically quite evident, as though existing polynuclears became more functional as a result of RLB administration. Usually, posology decrease or/and treatment's apart increase become systematic in these chemotherapy cases. Cytostatic agents extensively degrade the bone marrow [14]. This positive action of RLB might be attributed to the effect of this molecule on cell division [11, 12].

RLB systematic utilization should give best results for chemotherapy,

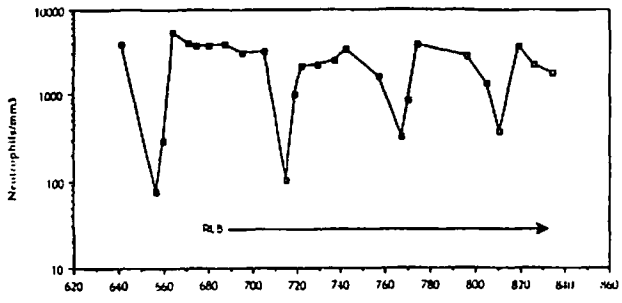

Fig. 1a

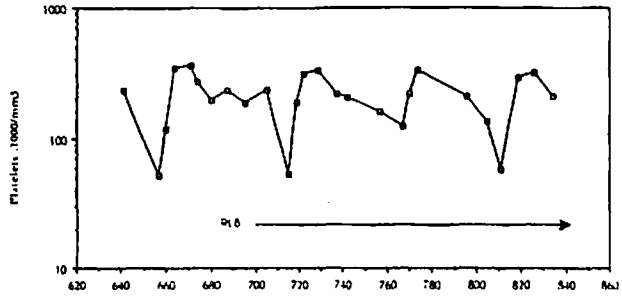

Fig. 2a

Fig. 1a + b: Decimal logarithm of polynuclear neutrophil count/mm^3 (a), platelet count x 10^3/mm^3 (b) according to cumulative days since the first day of the first cure for subject 1. Thanks to RLB administration, aplasia observed at first could be avoided for the following chemotherapy treatments and protocol could be regularly followed.

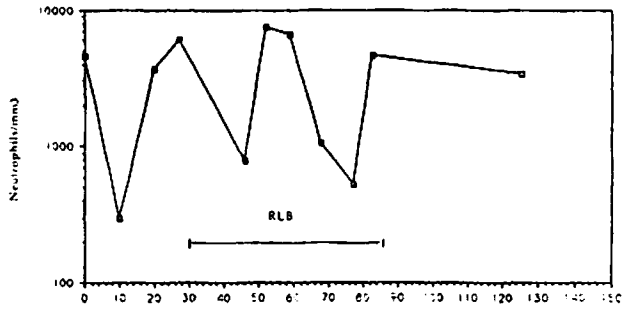

Fig. 1a

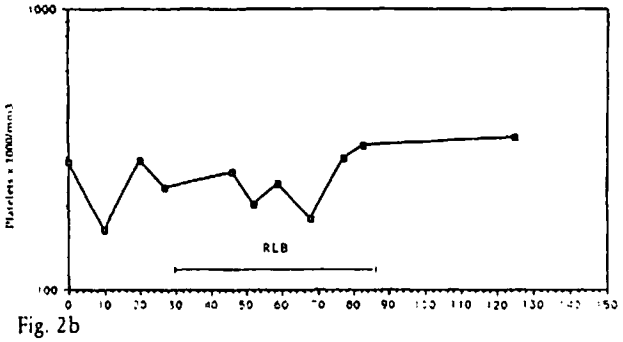

Fig. 2b

Fig. 2a + b: Decimal logarithm of polynuclear neutrophil count/mm^3 (b), platelet count x 10^3/mm^3 (b) according to cumulative days since the first day of the first cure for subject 2. Compared to initial cure, polynuclear neutrophils increased more rapidly when RLB was given to patient. RLB was supended on day 80, as patient went into hospital for thrombophlebitis in another city (where checkup on day 127 was performed).

particularly with non-Hodgkin malignant lymphoma. The complete treatments might be done with respect of treatment intervalls and administered on anticipated doxorubicin posology ratio equal to 1.

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