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Clinical report

Multicenter study of the impact of prescription guidelines on the use of colony stimulating factors

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The aim of this work was to assess the impact of circulating guidelines for correct prescription practices of colony stimulating factors (CSF). Two hospital groups were compared, a 'guidelines' group (seven teaching hospitals) that circulated the guidelines and a control group (eight teaching hospitals) that did not. In addition, two periods were compared before and after distribution of the guidelines: from 17 February to 2 March 1996 and from 17 February to 2 March 1997. The assessment involved compliance with the guidelines for the following parameters: indications, dose regimen, time to start of CSF therapy and duration of CSF therapy between the control and guideline groups and also between the two periods. The population included 404 patients analyzed (209 in 1996 and 195 in 1997) for the indication of post-chemotherapy neutropenia. Total compliance in the first period (all four items) was 44.2% in the control group and 50.8% in the guideline group (non-significant), and during the second period was 31.9 and 59.6% in the two groups ($p<0.001$). During the first period, the differences in compliance with the guidelines for indication, dose regimen, time to start of treatment and duration between the groups were not significant. In the second period, this difference became significant and in favor of the guideline group for dose regimen ($p=0.009$) and treatment duration ($p=0.02$). The results of this study show the need to continuously define prescription reference systems according to available data, and to circulate them widely to improve the quality of health care and to control expenses. [© 2000 Lippincott Williams & Wilkins.]

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Introduction

Colony stimulating factors (CSF) have been available for almost a decade and are indicated in primary or secondary prophylaxis of chemotherapy-induced neutropenia. CSF have been included in many chemotherapy protocols because they provide benefit with little associated risk. Because the high cost of these agents has a significant impact on the limited resources of health care systems, steps must be taken to optimize their prescription.

The American Society of Clinical Oncology (ASCO/evidence based) and the Fédération Nationale des Centres de Lutte contre le Cancer (National Federation of Anticancer Centers) (FNCLCC/consensus driven) have published guidelines to assist professionals in prescribing CSFs.[3–6]

The aim of the present work is to assess the effect of circulating guidelines prepared by our group based on existing references on the quality of prescribing CSF. This work was further justified by the economic impact of a possible misuse of these agents,[2] but it was not designed as an pharmaco-economic study. It should be viewed as an educational aid to inform prescribing physicians, and as a strategy to adapt and implement clinical guidelines to optimize prescription practices.

Materials and methods

Preparation of the guidelines

Seven pharmacists from different teaching hospitals developed algorithms for prescribing and delivering CSF. Evidence-based algorithms were developed for indications, time to start of CSF therapy and dosing regimen. Consensus-driven guidelines were developed for duration of treatment. The guidelines were developed in cooperation with hematologists and oncologists at the various hospitals.

Sources used to prepare the algorithms included the French Marketing Authority (MA) with the indications for the products in question, ASCO recommendations,[3–5] FNCLCC recommendations[6] and prescription/delivery algorithms drafted by pharmacists of La Pitié Salpétrière Hospital.[7]

The guidelines were defined as algorithms (Figure 1) and written tools (Table 1).

Content of guidelines

Indications for CSF. Febrile neutropenia was defined by a body temperature or 38.5°C or higher lasting more than 1 h and concomitant with a stage IV neutropenia as defined by the WHO, i.e. absolute neutrophil count (ANC) $<500/\mu l$.

The combination of a cytotoxic regimen was defined by the study of Closson *et al.*[7] According to ASCO recommendations, the prescription of CSF in primary prophylaxis is considered to be justified in the case of a combination of two cytotoxic agents at a dose regimen which induce a febrile neutropenia in 40% or more of the cases (Table 1). Lower chemotherapy doses are accepted when one anticancer neutropenic agent (as previous defined) was associated with two risk factors as indicated in Table 1.[7]

The prescription of CSF in secondary prophylaxis is considered as justified when stage IV febrile neutropenia had been observed during previous cycles.

The prescription of CSF during a curative therapy (patients having attained stage IV febrile neutropenia with high septic risk factors such as septic syndrome, lung infection, systemic fungal infection) is considered as justified, in compliance with the MA.

Time to start of CSF therapy, duration of CSF therapy and dosing regimen. CSF treatment was considered justified when it was implemented between 24 h and 5 days after the end of the chemotherapy cycle. The prescription of CSF was

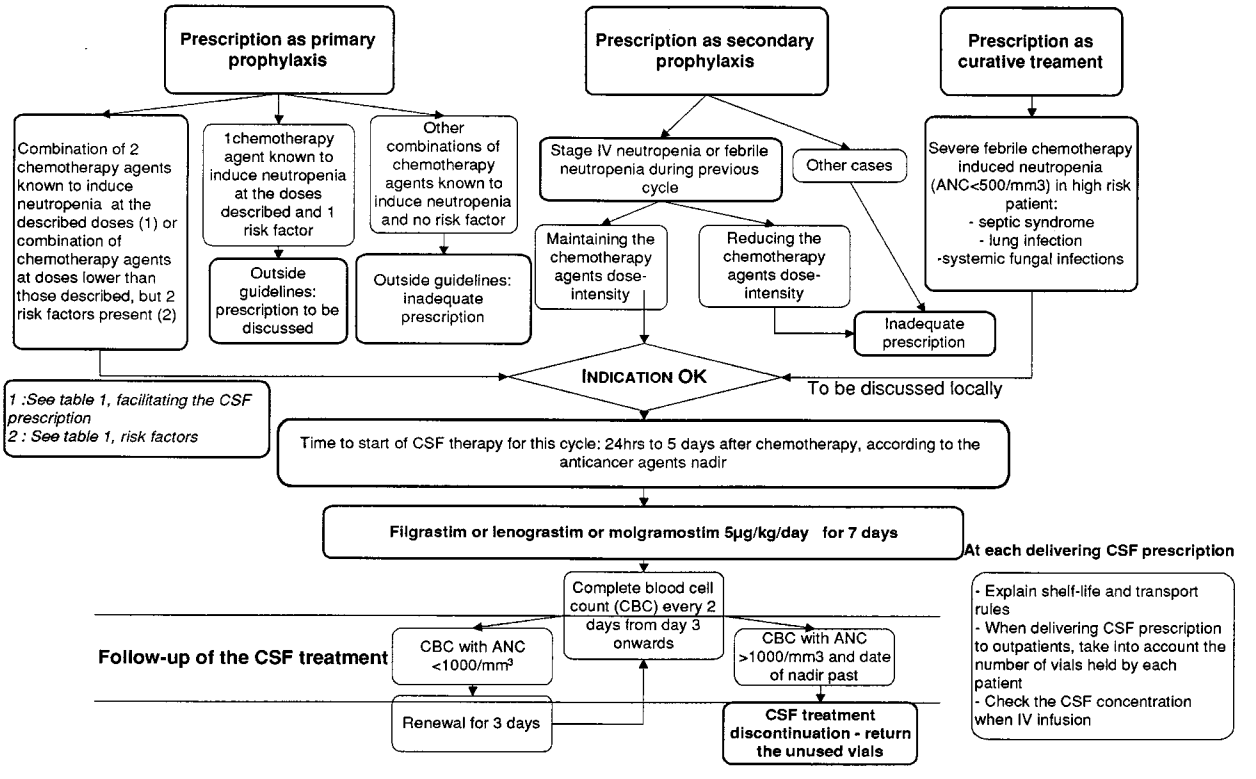

Figure 1. Algorithm: CSF prescription and delivering CSF prescription (anticancer chemotherapy).

Table 1. CSF Prescription with chemotherapy-induced neutropenia: effect of CSF prescription in chemotherapy-induced neutropenia (combination of at least two chemotherapy agents known to induce neutropenia at given doses)

Drugs	Combination of two chemotherapy-induced neutropenia dosage cycles (mg/m^2)	Combination of more than two chemotherapy-induced neutropenia dosage cycles (mg/m^2)	Nadir (days without CSF)	Recovery (day without CSF)
5-Fluorouracil	–	>2000	10	21–28
Amsacrine	>300	>300	7–10	21–28
Busulfan	>400	>400	11–17	42–56
Carboplatine	>400	>300	14–21	28–42
Chlorambucil	–	>80	21	42–56
Chlormethine	>12	>12	10–14	21–28/35
Cisplatine	>100	>100	14	21
Cyclophosphamide	>1000	>1000	7–14	21–28/18–25
Cytarabine	>500	>500	15–21	28–35
Dacarbazine	–	>400	21	28–35
Daunorubicine	>200	>200	10–14	21–28
Daunorubicine	>60	>60		
Docetaxel	>100	>100	7	
Doxorubicine	>50	>50	7–14	21/27
Epirubicine	>75	>75	7–14	21
Etoposide	>300	>300	7–14	21–28
Gemcitabine	>1000	>1000		
Idarubicine	>20	>10	10	21–28
Ifosfamide	>4500	>3000	7–14	21
Irinotecan	>350	>350	8	
Melphalan	–	>30	21	28–42
Methotrexate	>3000	>3000	7–10	14–24
Mitoxantrone	>12	>12	9–12	21–28
Paclitaxel	175	175	11	18
Pirarubicine	>50	>40	10–15	21–30
Procarbazine	–	>700	10–14/25–30	21–28/36–50
Teniposide	>200	>200	10–14	21
Thiotepa	>40	>30	10–14	21
Topotecan	>7.5	>7.5		
Vinblastine	>12	>10	5–10	14–21
Vindésine	–	>6	5–10	7–14
Vinorelbine	>60	>50	10	14–21

From Closson *et al.*[7] modified by the authors.
Risk factors: prior radiotherapy at at least two sites, prior autograft (bone marrow and stem cell transplant), AIDS, patient >65 years and prior chemotherapy prolonged more than six cycles with the last being less than 6 months.

not to exceed 7 days after which only an ANC $\leqslant 1000/\mu$l justified the continuation of treatment. If the ANC was $>1000/\mu$l, it was recommended to discontinue treatment. In a curative framework, the immediate implementation of treatment with no delay is justified.

The dose regimens used in this assessment were those of the MA. In primary/secondary prophylaxis and curative treatment the recommended dose was 5 μg/kg/day for all CSF. Vials containing 480 μg of filgrastim were reserved for patients weighing more than 60 kg.

Assessment of prescription compliance with guidelines

The impact of the guidelines was assessed by dividing the 15 participating teaching hospitals into two groups, having similar oncology and hematology activities. The guideline group (seven hospitals) included hospitals having issued guideline recommendations in their hospitals in January/February 1997. A control group (eight hospitals) did not circulate these recommendations.

Guideline distribution took place at a session of the hospital Drug Committee. Guideline task force pharmacists explained the process used to write the algorithms to the participating physicians. All guideline group hospital physicians were informed by broad mail circulation of the guidelines. The pharmacists of the guideline group hospitals informed the entire medical staff on an assessment before and after circulation, without detailing the period of data

collection. Two weeks before beginning data collection during the second stage of the study, a reminder of the guidelines was simultaneously issued in all hospitals of the guideline group.

In order to eliminate methodological bias,[9] both groups were compared during two identical time frames: from 17 February to 2 March 1996 and from 17 February to 2 March 1997.

Two pharmacists collected anonymous data from medical records and retrospectively analyzed them for the two periods. All patients treated with CSF during the study period were analyzed with no exclusion criteria. Each record was assessed for compliance with the guidelines. The use of CSF was considered appropriate if the five items (indication, product, dose regimen, time to start of treatment and treatment duration) were all compliant.

Statistical analysis was conducted using CDC EPI-INFO software, version 6.04 (1997). Inter-group and inter-period significance were determined with a χ^2-test at $\alpha < 0.05$.

Results

Population data

From a total of 423 prescriptions, 404 records were analyzed. Nineteen records were not available from medical records (10 in the control group and nine in the guideline group). The two groups were not homogeneous during the first period (77 records in the control group and 132 records in the guideline group). During the second period, there were 91 records in the control group and 104 in the guideline group. Between the two periods, there was a slight decrease in the number of prescriptions in the guideline group (132 versus 104), while this factor remained constant in the control group (77 versus 91).

Compliance study

Total compliance. Total prescription compliance during the first period was 44.2% in the control group (34 of 77) and 50.8% (67 of 132) in the guideline group. The difference was not statistically significant (p=0.43). Total compliance during the second period was 31.9% in the control group (29 of 91) and 59.6% in the guideline group (62 of 104). This inter-group difference was statistically significant (p=0.0002). The comparison of compliance between both periods revealed no significant difference in either group. Total compliance increased between the two periods in the guideline group and decreased in the control group.

Compliance by item. Out of the 404 post-chemotherapy neutropenia records, 365 were classified as primary and secondary prophylaxis and 39 as curative treatment. The principal findings are listed in Table 2.

Indication. The comparison of compliance with indication between the two periods was not significant for each group. Indication compliance increased between the two periods in the guideline group and remained stable in the control group. When the two groups were compared, the significance threshold was not reached.

Dose regimen. The comparison of compliance with dose regimen between the two periods was not significant for each group. No significant difference between groups was found in the first period. During the second period, the difference in dose regimen compliance between the two groups was significant (p=0.009). Non-compliance of dose regimen was only related to the use of filgrastim at the dose of 480 μg in patients weighing less than 60 kg.

Time to start for CSF treatment. Time to start of CSF therapy was taken into account only in primary and secondary prophylaxis, thus explaining why the number of records examined for this item differed from the others (365 versus 404). Conformity to the guideline remained stable for the two groups and periods, and was not statistically different. The inter-group and inter-period differences were not significant. The mean onset time during the first period was 2.7 ± 2.6 days in the control group and 3.1 ± 1.9 days in the guideline group. During the second period, mean onset time was 3.2 ± 2.6 days in the control group and 3.4 ± 2.2 days in the guideline group.

Treatment duration and renewal. The difference for compliance between the two groups during the second period was significant (p=0.02). Between periods 1 and 2, mean treatment duration decreased from 7.8 ± 3.1 to 7.3 ± 2.7 days in the control group and increased from 7.7 ± 3.4 to 8.1 ± 3.8 days in the guideline group (not significantly different).

After 7 days of treatment, compliance for renewal was low in the control group (17.6% in period 1 and 11.8% in period 2) and was higher in the guideline group (39.2% in period 1 and 48.6% in period 2). There was a statistically significant difference between the control and guidelines group for compliance with renewal at 7 days during period 2 (p=0.03) and period 1 ($p < 0.01$).

Table 2. Compliance with indication, dose regimen, onset of CSF treatment, treatment duration and renewal (%) (post-chemotherapy neutropenia, *N*=404)

	Period 1		Period 2	
	Control group	Guideline group	Control group	Guideline group
	(*N*=77)	(*N*=132)	(*N*=91)	(*N*=104)
Compliance with indication				
primary prophylaxis	39/56	64/82	37/54	61/76
secondary prophylaxis	11/14	23/34	22/30	15/19
curative treatment	3/7	8/16	2/7	3/9
Total	53	95	61	79
	68.8%	71.9%	67%	75.9%
Comparison between groups	NS		NS	
Compliance with dose regimen	75	125	85	104
	97.4%	94.7%	93.4%	100%
Comparison between groups	NS		p=0.009	
Compliance with treatment duration	49	99	61	86
	63.6%	75.0%	67.0%	82.7%
Comparison between groups	NS		p=0.02	
	(*N*=70)	(*N*=116)	(*N*=84)	(*N*=95)
Onset of CSF treatment	53	105	75	83
	75.7%	90.5%	89.3%	87.4%
Comparison between groups	NS		NS	
	(*N*=34)	(*N*=51)	(*N*=34)	(*N*=35)
Compliance with renewal, after 7	6	20	4	17
days of treatment	17.6%	39.2%	11.8%	48.6%
Comparison between groups	p=0.03		$p<0.01$	

Discussion

To assess the impact of guidelines for implementing treatment with CSF, a non-randomized pre- and post-controlled evaluation of the procedure was used. The inclusion of a control group avoided the introduction of bias resulting from the rapid development of oncology progress and practices.

During the first period, the overall percentage of prescription compliance with the criteria of indication, dose regimen, duration and time to start of CSF treatment was 44% in the control group and 51% in the guideline group. There was, therefore, a positive impact of the distribution of our guidelines.

Compliance between the two periods increased in the guideline group (+17.3%) and decreased in the control group (−27.8%). This change in compliance increased inter-group differences, making them significant in the second period in favor of the guideline group.

During the first period, poor total compliance of CSF prescriptions suggested a loss of knowledge 3 years after the first publication of ASCO recommendations and their circulation to both groups. Compliance continued to decrease in the control group. The guidelines served as a reminder and to update these recommendations in the guidelines group.

The analysis of each of the four items (indication, dose regimen, time to start of CSF therapy and duration of CSF treatment) helped to more precisely define the impact of recommendations in the post-chemotherapy indication (primary, secondary and curative treatment). The percent compliance for indications was relatively high in our study, ranging from 67% in the control group to 76% in the guideline group in the prospective study, whereas it was only 57% in a study carried out by an Australian group[10] with comparable compliance criteria. More stringent MA requirements and a delivery control system might explain initial compliance with indications in France.

If compliance for indications of prescription in the control group were adjusted to that of the guideline group, this would produce a savings of $0.25 M annually (calculated on the basis of yearly hospital consumption in the control group), as compared with the $3.2 M cost of CSF use in this group (7.8% of the total expenditure for CSF).

The algorithm was used to assess the compliance of CSF prescription in prophylactic situations when two neutropenic agents were used. In 65 cases, non-

compliance of CSF prescription was due to chemotherapy carried out with only one neutropenic anticancer agent at the described doses (Table 1). This occurred due to the lack of a precise definition of chemotherapy agents known to induce neutropenia given by the MA indications.

The time to start of CSF treatment was compliant with the guidelines in both groups and both periods. When prescribing at 3 days or more after chemotherapy, the aim of physicians was to maximize the effect of CSF during the nadir, occurring on the average at days 5 or 6 post-chemotherapy (Table 1). This is a pragmatic approach, since no randomized post-chemotherapy study has yet assessed the effect of this factor on the reduction of neutropenia. It was an adjustment of clinician's practices not mentioned in the guidelines.

Recommendations had a significant impact on treatment duration (p=0.02) and dose regimen (p=0.009) in the guideline group during the second period for treatment of chemotherapy-induced neutropenia where records were most numerous. Even though not studied to any great extent, these two items are extremely important because of their high economic impact, although both MA data and ASCO guidelines poorly define them.

The mean duration of post-chemotherapy CSF administration in our study was 7.8 ± 3.4 days in the retrospective period and 7.8 ± 3.7 days in the prospective period. Compared with the MA that authorizes a 14 day treatment, there is a current trend towards reducing the duration of treatment. Other studies have reported similar mean treatment duration, e.g. 9 days for Yim *et al*. in 1995.[13]

Our study is unique in that it defines prescription renewal criteria based on the ANC after 7 days of CSF therapy. Compliance with renewal thus defined was poor in the control group during the two periods, revealing a difference in favor of the guideline group. The follow-up of CSF treatment is based on the ANC count. Non-compliant prescriptions revealed an absence of the ANC rather than a continuance of the prescription with ANC $> 1000/\mu$l.

A better-targeted clinical surveillance (ANC every 2 days after 7 days of treatment) would help limit unjustified CSF expenses. In terms of health economics, the direct cost of hematological examinations is clearly lower than the daily cost of CSF therapy in France ($12 versus $100). This optimization should be developed with medical/pharmaceutical cooperation in an approach focused on the follow-up of outpatients as described by the pharmaceutical care process.

Concerning the criteria of dose regimen, however, we recorded no significant difference between the two study periods.

Without considering compliance, the total number of prescriptions (all indications taken together) decreased by 13% between the two periods in the guideline group, while it increased by 9.5% in the control group. This change is even more noteworthy in that, during the period studied, oncology activity increased 12.3% in the CSF group and 7.2% in the control group.

The decrease in yearly CSF expenditure confirms this tendency. Expenditure for CSF decreased from $4.25 to $3.12 M between 1996 and 1997 (a 26.9% decrease) in the guidelines group, while in the control group it decreased from $3.45 to $3.20 M during the same period (a 7.2% decrease), with no change in the unit cost of drugs.

This decrease reflects a lack of prescription in some medical situations in the guideline group where prescriptions would have been considered as complying with the guidelines.

Conclusion

The circulation of guidelines concerning CSF prescriptions was accompanied by an increase in prescription compliance in the guideline group compared to the control group. Our guideline group sent prescription algorithms and written tools to help the follow-up of the prescription of CSF therapy in the hospitals of the control group.

This study is part of the current approach of assessing hospital practices and its usefulness will be effective only it is if accompanied by a long-term follow-up, including a broad circulation of results and algorithms, and a renewal of prescription assessments. This study demonstrates the value of implementing medical/pharmaceutical task forces to design tools for measuring prescription quality and drug delivery.

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