**Bacteriology**

**VALUE OF SPUTUM EXAMINATION IN PREDICTING PROGNOSIS DURING SHORT COURSE CHEMOTHERAPY**

Sujatha Chandrasekaran*, R. Rajalakshmi** & P. Jagota***

**Introduction**

Bacteriological examination of sputum is known to be the best tool for monitoring the efficacy of chemotherapy for pulmonary tuberculosis: mycobacterial culture being the ideal with its ability to differentiate between the dead and live organisms. The disadvantages of mycobacterial culture examination are well understood. It is time consuming, expensive, needs special equipments and high quality trained technicians. Hence, it is rarely used for diagnostic purposes. It has a role in predicting the outcome of treatment, but the prospect of its use on a routine scale in developing countries for this purpose is very doubtful.

In contrast, sputum smear examination is a simple and cheaper procedure. It is widely used and is also the tool of choice under the District Tuberculosis Programme (DTP). In the case of conventional chemotherapy regimens, smear examination at six months of chemotherapy is a good prognostic indicator and culture may not yield additional information. However, under Short Course Chemotherapy (SCC), because of the rapid killing of bacilli by drugs, sputum is presumed to have more of non-viable bacilli giving higher chances of a microscopy positive, culture negative phenomenon. Hence, it is not known how a smear examination would be useful during the course of SCC for the purposes of prognostication. Culture conversion to negativity at the end of two months therefore appears to be the best as an early indicator of the efficacy of chemotherapy, as observed in controlled clinical trials. However, in view of the obvious limitations of widespread use of culture as a tool for case follow-up, it would be worthwhile to see to what extent smear examination could fill in the role. This paper examines the value of smear microscopy after two months of chemotherapy for the purpose of predicting the final outcome of treatment.

**Material & Methods**

**Patients**

A total of 530 newly diagnosed patients of smear positive pulmonary tuberculosis, aged 12 years and above had constituted the study material for two of the operational investigations carried out by the National Tuberculosis Institute (NTI), Bangalore for evaluating the efficacy of SCC regimens under conditions of the DTP. Two regimens that were used in the study were 2EHRZ/6TH (EH) [regimen 1] and 2SHR/4HR [regimen 2]. Of these patients, the availability of bacteriological results from all the follow-up examination during the course of treatment were limited to 256 and are considered for analysis.

**Investigations**

**Sputum collection**

Two samples, one spot and one over-night were collected at the beginning of the chemotherapy. Follow-up examination was done at the end of two months and again at the end of chemotherapy.

**Culture and sensitivity tests**

The sputum specimens were subjected to acid-fast microscopy by Ziehl-Neelsen (ZN) method, culture by modified Petroff’s method and drug sensitivity tests as per routine.

**Analysis**

Chi-square “X²” test was used for statistical analysis.

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Table 1

Bacteriological status of initially positive cases at second month and at the end of treatment for two regimen groups

<table>
<thead>
<tr>
<th>Bact. status 2nd month (culture/smear)</th>
<th>Bacteriological status at the end of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R1 Total</td>
</tr>
<tr>
<td>C+ S+</td>
<td>9</td>
</tr>
<tr>
<td>C- S-</td>
<td>99</td>
</tr>
<tr>
<td>C+ S-</td>
<td>3</td>
</tr>
<tr>
<td>C- S+</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
</tr>
</tbody>
</table>

(Proportion of favourable response is indicated in parenthesis)

The four different groups considered for the analysis are based on the culture and smear results. They are as follows:

- C+S+ (culture & smear positive), C S+ (culture negative, smear positive), C+S (culture positive, smear negative) and C S (culture and smear negative). These results are correlated with the favourable response at the end of chemotherapy, which is defined as culture negativity.

Results

Table 1 gives the number of patients in each group at the end of two months as against their status at the end of chemotherapy with the two regimens employed. It can be seen that a majority of patients had converted to culture as well as smear negative status at the end of two months with either of the regimens.smear negative status at the end of two months with either of the regimens.

Both the regimens had given a favourable response of 80%, the difference between them being not significant. It can be seen that among patients who were negative by smear and culture at the end of two months, the final conversion was 82.9% with regimen 1, 89% with regimen 2 and 85.4% with both. The persons harbouring non-viable bacilli at the end of the second month (C S+) were 16% (41 out of 256); favourable response among this group was 85.4%.

The different categories, when regrouped as in table 2, either by their culture or smear results considered singly, showed that though smear positives at two months had a higher proportion of favourable response (71%) at the end of chemotherapy than culture positives (53.5%), the differences were not statistically significant.

Table 2

Favourable response among different groups

<table>
<thead>
<tr>
<th>Bact. status 2nd month (by any method)</th>
<th>Favourable response at the end of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>S+</td>
<td>62</td>
</tr>
<tr>
<td>C+</td>
<td>43</td>
</tr>
<tr>
<td>S-</td>
<td>194</td>
</tr>
<tr>
<td>C-</td>
<td>213</td>
</tr>
</tbody>
</table>

Table 3

Agreeing and disparate groups with respect to culture & smear results

<table>
<thead>
<tr>
<th>Bact status 2nd month</th>
<th>Favourable response at the end of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1 No.</td>
<td>%</td>
</tr>
<tr>
<td>Disparate (C+S+ &amp; C-S-)</td>
<td>18</td>
</tr>
<tr>
<td>Agreeing (C+S+ &amp; C-S-)</td>
<td>85</td>
</tr>
</tbody>
</table>
Table 3 gives the favourable response among two groups: agreeing and disparate ones with regard to their culture and smear results. The percentage of patients who showed favourable response are 77.8% and 80.8% in the disparate and agreeing groups respectively.

Even when smear negativity was to be taken as favourable response, the S+ group gave a smear conversion of 67.7% (42/62) which was not significantly different from culture negativity (71%) [not shown in table]. It can also be observed that patients who had converted at the end of two months (intensive phase), had a considerable chance of continuing their negative status at the end of treatment, irrespective of the level of chemotherapy, provided they had successfully completed the intensive phase (level 3 or level 4) [not shown in table].

**Discussion**

In this paper, data from two similar studies have been taken into consideration and clubbed which is an accepted mode of analysis while seeking an answer to a common problem6. This analysis facilitates combining of results from a number of studies carried out in a similar manner examining similar questions and is called “meta analysis”.

Following questions are examined in this paper:

1. What is the efficiency of smear in comparison to culture examination, carried out at the end of two months of treatment in predicting the final outcome of chemotherapy?

2. What is the proportion of patients excreting non-viable bacilli at the end of two months of SCC, as this is said to be a common phenomenon?

The inference made from the results are:

1. In case the smear was negative at the end of two months, it had a predictive value of forecasting favourable response to the extent of 83%; if positive, it dropped to 70% (p<0.05). This implies that 83% of the patients who were smear negative at two months (irrespective of culture result at that stage) would convert to culture negativity at the end of chemotherapy (disregarding the smear result on completion of treatment). On the other hand, 70% of cases who were smear positive in second month (irrespective of culture result at that stage) were found to be culture negative at the end of chemotherapy (disregarding the smear result on completion of treatment). Hence, smear positivity at the end of 2 months, by itself, could not be considered to bode an unfavourable prognosis, whereas negativity had a good probability of a favourable outcome. The smear results at second month were not significantly different from culture results. Hence, smear microscopy in SCC gave as reliable a result as culture both during and at the end of chemotherapy.

2. Among the patients put on SCC, 16% excreted non-viable bacilli at the end of the intensive phase. Of them 85.4% converted to smear negativity at the end.

The above findings confirm the hypothesis that a properly conducted smear microscopy is as good as culture examination for diagnostic as well as prognostic purposes under operational conditions.

The present analysis indicated that completion of intensive phase of treatment is a crucial objective and intermediate sputum examination results are not highly relevant in predicting the results among those who have completed the treatment. This is true for both smear as well as culture examinations performed at the intermediate stage. Hence, more efforts should be directed towards prevention of defaults during the intensive phase through proper motivation, prompt defaulter action, maintenance of adequate drug supply, proper and timely management of side effects etc. Concerted effort should be made to achieve successful completion of the intensive phase. By ensuring proper drug supply thereafter, it could be predicted that a high proportion of favourable response could be obtained.

It is of interest to learn that in some countries, the policy is to perform smear microscopy at the end of two months and in case of a positive result, to extend the intensive phase by one more month. It is also favoured by the WHO because of possible operational advantages. However, implementation of the policy everywhere in India requires a substantial increase in the cost of chemotherapy. It also increases the workload on health services. Moreover, the rationale of extending the intensive phase by one more month for those who remain smear positive at the end of two months of treatment is difficult to see, unless the reasons for such positivity are clearly analysed and remedied first. The present analysis
has indicated that 41 out of 62 of such patients were actually excreting nonviable bacilli, suggesting that in most of them, extension of intensive phase could not be seen as a rewarding step. It adds to costs, asks patients to consume drugs for longer duration and might in addition, attract unforeseen problems. More studies are suggested on the observations made in this paper, so that treatment priorities are assigned appropriately on scientific evaluation of risks of non-conversion.

Summary

Culture examination of sputum is known to be the best tool for assessing the prognosis in patients of pulmonary tuberculosis. Controlled clinical trials with SCC have shown that culture examination of sputum at the end of two months elicited a high degree of conversion. But, it is not possible to provide sputum culture facilities in the DTP. Since smear examination facilities is widely available under the DTP, this paper examines the comparability of results obtained with it in patients on SCC, with culture. It also examines the value if any, of an early evaluation of the treatment result in patients on SCC by smear examination at two months under operational conditions. Data from two operational studies on SCC are utilised for this purpose. Of a total of 256 patients, 62 were smear positive at the end of two months, but 41 (16%) of them were excreting nonviable bacilli. Nevertheless, in predicting the final outcome of chemotherapy, no significant difference was observed between smear and culture examination at the end of two months.

Acknowledgements

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