Antiproliferative Effects of Idoxifene in a Placebo-controlled Trial in Primary Human Breast Cancer

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ABSTRACT

Idoxifene is a novel selective estrogen receptor modulator. It has reduced agonist activity on breast and uterine cells compared with tamoxifen and antiproliferative effects in tamoxifen-resistant breast cancer cells. Previous studies have shown that a short course of treatment with other antiestrogens prior to surgery caused a significant reduction of the growth fraction when measured by immunohistological staining using the mouse monoclonal antibody Ki67. In this study, we assessed the effect of idoxifene on biological markers of cell proliferation (Ki67) and apoptosis (TdT-mediated dUTP-biotin nick end labeling), and estrogen and progesterone receptor (ER/PR) expression was also evaluated. Core-cut biopsies were obtained in 77 postmenopausal patients with primary breast cancer at diagnosis. Patients were randomized to 40 mg/day idoxifene or placebo for 14–21 days prior to obtaining a second biopsy sample at surgical resection. The percentage of Ki67-labeled cells fell from a mean 19.7 ± 2.7% (SE) to 13.4 ± 3.4% in idoxifene-treated ER-positive tumors (n = 30; P = 0.0043), but there was no significant effect in placebo-treated ER-positive tumors (n = 27). No effect was seen on ER-negative tumors in either group. Idoxifene had no significant effect on apoptotic index but produced a statistically significant fall in idoxifene-treated ER immunohistochemical score and a small increase in PR that did not reach statistical significance (0.05 < P < 0.10). Idoxifene was well tolerated in all patients. Idoxifene has an antiproliferative effect in ER-positive but not ER-negative breast cancers, and no significant effect on apoptosis in the short-term.

INTRODUCTION

Idoxifene is a novel SERM2 that recently has been evaluated for the treatment of advanced breast cancer (1, 2). Idoxifene is the 4-iodo-substituted analogue of tamoxifen, synthesized using rational drug design to decrease the estrogen agonist activity and increase the estrogen antagonist activity of the parent compound (3). Compared with tamoxifen, idoxifene has been found to be metabolically more stable and to have a higher relative binding affinity for the ER. It also has reduced agonist activity on breast and uterine cells, greater in vitro activity than tamoxifen, and an antiproliferative effect in tamoxifen-resistant breast cancer cells (3).

At present there are limited data on idoxifene’s anti-breast cancer activity. In phase I studies, metastatic breast cancer patients have received idoxifene at doses of 10–60 mg/day for 1 week followed by treatment at a dose of 20 mg/day until disease progression. Evidence of response was seen in 2 of 14 patients in one study and 3 of 10 patients in a second (2). In a phase II study comparing 40 mg/day idoxifene and 40 mg/day tamoxifen, idoxifene was associated with evidence of clinical activity in patients with tamoxifen-resistant advanced breast cancer. Similar safety profiles were seen with both compounds (1).

At doses of 5 and 10 mg/day, idoxifene produced a significant reduction in biochemical markers of bone turnover in postmenopausal women (4). Significant reductions were also observed in total cholesterol, low-density lipoprotein, and total cholesterol/high-density lipoprotein ratio (5). Thus, idoxifene has the properties of a SERM: it expresses antagonist activity in breast cancer cells and a low level of agonist activity on the uterus (in model systems) coupled with agonist activity on bone and lipid metabolism.

It would be valuable to establish during early clinical development of SERMs (and other agents) the growth-suppressant effects of specific drug dosages and the subpopulations of tumors in which these effects occur. We report a study that explored the efficacy of idoxifene in breast cancer by means of the evaluation of biological markers of tumor proliferation (Ki67 labeling index) and apoptotic index in patients scheduled for surgery with primary breast cancer. ER and PR expression were also evaluated both as predictors of response and markers of antiestrogenic effects.

Earlier studies have shown that a short course of treatment with tamoxifen or the pure antiestrogen ICI 182780 prior to surgery caused a significant reduction in the Ki67 labeling index of primary breast tumors (6, 7). Recent work has demonstrated that responders but not nonresponders to tamoxifen therapy...
show a significant decrease in Ki67 after 14 days (8). Thus, changes in proliferation in response to short-term challenge with an antiestrogen may be predictive of clinical effectiveness.

Significantly higher levels of apoptosis have also been found in human tumors during their treatment with tamoxifen or ICI 182780 (9). This confirms the observations of estrogen deprivation-induced apoptosis found in xenograft studies (10, 11), and these findings recently have been extended by demonstrating that idoxifene itself induces apoptosis in xenograft systems (12). Thus, induction of apoptosis may also be a marker of pharmacological effectiveness of endocrine therapy. It is well established that breast tumor ER and PR expression is predictive of pharmacological effectiveness of endocrine therapy. Response to antiestrogen therapy in human breast cancer has been observed in ~50% of patients with ER-positive tumors and 75% that are positive for both ER and PR (13).

MATERIALS AND METHODS

Study Design. This was a multicenter, randomized, double-blind study in postmenopausal women with primary breast cancer. Written informed consent to participate in the study was obtained from all patients before enrollment. Patients received medication with 40 mg/day idoxifene p.o. versus placebo for ~14 days prior to surgery, to a maximum of 21 days. Tumor biopsy samples were taken before the start of treatment and at surgery for the measurement of Ki67 labeling index, apoptotic index, and ER and PR expression. Clinical assessments and laboratory tests were performed to evaluate the tolerability of study treatment. The protocol was approved by each local Ethical Committee.

Inclusion and Exclusion Criteria. Postmenopausal female patients were enrolled. Postmenopausal status was defined as >12 months since last menses; in patients whose last menses was ≤12 months before the start of treatment and in patients who were amenorrheic as a result of surgery, follicle-stimulating hormone and luteinizing hormone levels were to lie in the postmenopausal range (follicle-stimulating hormone >35 IU/L; luteinizing hormone >40 IU/L). Patients had to have a histological or cytological diagnosis of primary breast cancer and an operable lesion ≥2 cm in size. Lesion sizes of <2 cm could, however, be considered if, in the investigator’s opinion, a good quality core-needle biopsy could be obtained using a 14-gauge needle. Grading was performed by central review by a single pathologist (Dr. N. Nasiri, Royal Marsden Hospital, London, United Kingdom) on the excision biopsy specimen. Patients were enrolled only if they had a performance status ≤2 (Eastern Cooperative Oncology Group-WHO scale), a life expectancy of ≥4 months, and no known renal or hepatic impairment. Patients with metastatic breast cancer (stage IV) or who had received prior therapy for breast cancer or with previous malignancies within the last 5 years at other sites were excluded. Other exclusion criteria were concurrent medical or psychiatric problems unrelated to breast cancer; treatment with another investigational drug; concomitant treatment with hormone replacement therapy, coumarin-type anticoagulant therapy, or oral or i.v. corticosteroids; and a known hypersensitivity to tamoxifen or tamoxifen analogues.

Study Procedures. Patients were screened within 2 weeks prior to receiving study medication to determine eligibility for entry into the study. Eligible patients were randomized to receive a blinded treatment regimen of either idoxifene or placebo and were then evaluated clinically prior to surgery and 1 week after surgery/withdrawal. The following procedures were carried out: complete medical history and physical examination, hematology and blood chemistry evaluations; 12-lead electrocardiogram, chest X-ray, computed tomography or magnetic resonance imaging scan, or ultrasound if clinically indicated. Documentation of lesion size, and histopathological type and grade were performed on the tumor excision biopsy obtained at surgery. Clinical assessments and laboratory tests were performed to evaluate the tolerability of study treatment. In the safety evaluation, clinical interpretation was based on review of displays of adverse experiences. Principal considerations in this evaluation were time to onset, severity, study medication, and investigator-reported relationship of an adverse experience with the study medication.

Primary and Secondary Efficacy Variables. The primary study end point was the change in Ki67 tumor proliferation score from pretreatment to posttreatment biopsy. Secondary efficacy variables were the changes in apoptotic index, and ER and PR expression from pretreatment to posttreatment.

Study Medication. Idoxifene was supplied as white, circular, biconvex tablets containing 40 mg of idoxifene. Placebo tablets were of identical appearance. Study medication was provided in plastic bottles containing 21 tablets of either idoxifene or placebo. The bottles were labeled with information including protocol number, job number, patient number, directions for use, the quantity of tablets supplied, warning statements, and storage conditions. Patients took one tablet (either 40 mg of idoxifene or placebo) p.o. once a day for 14–21 days. No instructions were given with respect to the timing of study medication in relation to meals. Treatment duration was dependent on the date of surgery. Patients continued on the study drug for a minimum of 14 days to a maximum of 21 days. Surgery was to take place within 21 days of commencing study medication. At each study site, patient numbers were randomly linked to packaged medication supplies. The medication code was to be broken only in the event of a serious adverse experience that the investigator could not adequately treat without knowledge of the identity of study medication. The numbers of bottles and tablets dispensed for each patient were maintained and reconciled with the study medication record.

Tumor Samples. Before the start of study medication, a core-cut biopsy of the primary breast tumor was obtained using a 14-gauge needle, and at surgery a representative sample of the excision tumor was obtained from the operative specimen. Both specimens were fixed in 10% neutral buffered formalin and embedded in paraffin wax. The embedded blocks were sent to the Royal Marsden Hospital, London, United Kingdom for processing and analysis. Sections (3 μm thick) of the paraffin wax blocks were cut onto positively charged slides and dried overnight at 37°C before being used to determine Ki67, apoptosis, ER, and PR by previously published immunohistochemical methods.

Analytical Methods. Measurement of cell proliferation was by immunocytochemical assay using the MIB1 mouse monoclonal antibody to Ki67 (14). Ten high-powered fields were scored. Measurement of apoptosis was by TdT-mediated
RESULTS

Biomarker Data. Except where stated, all data below relate only to the efficacy evaluable population, i.e., ER positive and eligible for all criteria. The changes in biomarkers are summarized in Table 2.

Ki67 Labeling Index. Individual changes in Ki67 between the two biopsies for both placebo and idoxifene are

dUUT-biotin nick end labeling; the apoptotic index was expressed as a percentage: (no. of cells displaying apoptotic bodies × 100) ÷ (total no. of cells) (14). Three thousand tumor cells/section were counted for apoptotic index. Demonstration of ER expression was by the Novocastra 6F11 mouse monoclonal antibody (15) and of PR was by the Novocastra 1A6 antibody (11). ER and PR expression was assessed semiquantitatively by determining the percentage of tumor cells stained by the primary antibody and assessing the intensity of staining, using a score of 0 to 3, which corresponded to negative, weak, intermediate, and strong staining intensities in 10 high-powered fields. The percentage of tumor cells in each of these categories was used to calculate the overall H-score, ranging from 0 to 300. Tumors with a score ≥20 were considered positive for either ER or PR. In all cases, pairs of samples from the same patient were stained and scored in the same assay batch. Scoring was conducted by one analyst (M. H.) and was subject to quality control checks by a second (J. S.).

Statistical Analysis. Study participants were randomly assigned to receive either 40 mg of idoxifene or placebo using the technique of randomly permuted blocks.

A total of 50 patients (25 per arm) with positive ER status were to be recruited for this study. It was expected that ~70 patients would need to be enrolled to achieve this number because in most cases ER status would be unknown at the time of study entry. The sample size was based on those of previous studies reporting decreased Ki67 levels after presurgical treatment with antiestrogens (6, 7). Patients were considered to have completed the study as planned and to be evaluable if they met all eligibility criteria, were found to be ER positive, and had both pre- and posttreatment biopsies taken that contained sufficient tumor cells for analysis (efficacy evaluable population).

The primary efficacy evaluation was based on the Ki67 tumor proliferation score. The arithmetic difference between scores obtained from the pretreatment needle biopsy and excised tumor biopsy were determined for each patient (described as absolute change). These differences were compared by a Mann-Whitney nonparametric analysis. Similar analyses were performed for the apoptotic index, ER, and PR.

Evaluation of safety data included all randomized patients (ITT population) and were summarized as descriptive statistics.
The mean change was no significant effect in the placebo-treated ER-positive tumors: a labeling index of 17.6 from the data analysis resulted in a mean pretreatment Ki67 respectively. There was no evidence of technical failure being responsible for these extreme results. Exclusion of this patient from the data analysis resulted in a mean pretreatment Ki67 labeling index of 17.6 ± 1.7% and posttreatment index of 10.7 ± 2.2%, with a mean change of −6.8 ± 1.9%. There was no significant effect in the placebo-treated ER-positive tumors: the mean change was +1.0 ± 1.4%.

The numbers of ER-negative patients was small (n = 13). Pretreatment Ki67 levels were higher in the ER-negative group (mean, 36.9%), and there was no significant change in levels with either idoxifene (n = 6) or placebo treatment (n = 7).

Patients positive for both ER and PR in the idoxifene-treated group showed a mean fall from 18.6 ± 3.5% to 11.5 ± 4.2%, giving a mean change of −7.1 ± 1.6% (P = 0.0034; Fig. 2). Excluding patient A from this analysis led to a change from 15.5 ± 1.5% to 7.5 ± 1.4%, a mean change of −7.9 ± 1.4%. Thus, the decrease as a proportion of the baseline was greater in the ER-positive/PR-positive group than in the ER-positive group as a whole.

**Table 2** Summary of mean (±SE) biomarker values before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Ki67 (%)</th>
<th>Apoptotic index (%)</th>
<th>PR (H-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PR+ only</td>
<td>All&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>18.8 ± 2.3</td>
<td>17.4 ± 2.5</td>
<td>0.80 ± 0.08</td>
</tr>
<tr>
<td>Post</td>
<td>19.8 ± 2.2</td>
<td>18.3 ± 2.7</td>
<td>0.85 ± 0.07</td>
</tr>
<tr>
<td>Change</td>
<td>+1.0 ± 1.4</td>
<td>+0.9 ± 1.9</td>
<td>+0.04 ± 0.05</td>
</tr>
<tr>
<td>n</td>
<td>27</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Idoxifene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>19.7 ± 2.7</td>
<td>18.6 ± 3.5</td>
<td>0.88 ± 0.09</td>
</tr>
<tr>
<td>Post</td>
<td>13.4 ± 3.4</td>
<td>11.5 ± 4.2</td>
<td>0.90 ± 0.09</td>
</tr>
<tr>
<td>Change</td>
<td>−6.3 ± 1.9</td>
<td>−7.1 ± 1.6</td>
<td>+0.02 ± 0.05</td>
</tr>
<tr>
<td>n</td>
<td>30</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>P&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.0043</td>
<td>0.0034</td>
<td>0.72</td>
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</tbody>
</table>

<sup>a</sup> All subjects within each group, regardless of PR status.

<sup>b</sup> P for the comparison of the change for each analyte between the placebo and idoxifene.

**Fig. 1** Individual changes for percentage of Ki67 for the placebo (left) and idoxifene (right) ER+ groups. One patient in the idoxifene group had pretreatment and on-treatment values of 82.3% and 91.7%, respectively, and is not plotted (shown as dashed line). Pre, pretreatment; D14/21, 14–21 days of treatment.

**Apoptotic Index.** Individual changes in apoptotic index between the two biopsies are shown for both placebo and idoxifene in Fig. 3, and the mean changes are shown in Table 2. The mean difference between pretreatment and on-treatment samples was very small for both the idoxifene group (+0.02 ± 0.05%) and the placebo group (+0.04 ± 0.05%). The difference between the two treatment groups was not statistically significant index (P = 0.7200), showing that idoxifene had no significant effect on the apoptotic index. The mean pretreatment level in the ER-negative group was higher than in the ER-positive group (1.6% and 0.9%, respectively). The ER-negative patients showed no effect of either therapy on the apoptotic index. There was no significant increase in apoptosis after idoxifene treatment in tumors positive for both ER and PR (P = 0.99).

**ER and PR Expression.** Individual changes in ER and PR expression between the two biopsies are shown for both placebo and idoxifene in Figs. 4 and 5, and the mean changes are shown in Table 2. At the end of therapy, the ER expression in the idoxifene-treated patients decreased. A slight decrease was also observed in the placebo-treated group, but the change was significantly greater for the idoxifene-treated group (P = 0.027).

Considering all patients, PR expression showed a minor mean increase in the immunohistochemical score in the idoxifene-treated group with very little change in the placebo group. The difference in the change between the two groups did not
reach statistical significance ($P = 0.078$). However, in those patients who were PR positive prior to treatment, there was an increase in the H-score of $26 \pm 10$ in the idoxifene group and a decrease in the placebo group of $2 \pm 8$, showing a significant interaction with treatment ($P = 0.0002$).

Safety. Idoxifene was well tolerated. Seven patients in the idoxifene group and six in the placebo group had adverse experiences considered by the investigator as suspected as being or probably related to study treatment. The most frequently reported adverse event was hot flushes of mild intensity in three patients in the idoxifene group and dyspepsia in two patients in the placebo group. There were very few laboratory abnormalities in patients randomized to study medication, and all were considered as clinically nonsignificant.

**DISCUSSION**

Significant reductions in Ki67 labeling index in primary breast carcinomas have been reported previously after short-term, presurgical treatment with tamoxifen or the pure anti-estrogen ICI 182780 (6, 7). No previous studies have been conducted with idoxifene, but it has been shown to lead to reduced Ki67 levels in MCF7 human breast cancer xenografts (12).

In this study, idoxifene led to a pronounced change in mean Ki67 in ER-positive but not ER-negative patients. Overall in the idoxifene-treated ER-positive patients, the fall was to $\sim 65\%$ of baseline levels. Comparison of these changes with those reported in the earlier studies with other antiestrogens is not valid because, as well as being in different populations, those studies used a different antibody to Ki67 in frozen rather than formalin-fixed biopsies. Nonetheless, the data indicate that idoxifene, like these other two drugs, should be an effective anti-breast cancer drug in ER-positive patients.

The lower Ki67 in the ER-positive group and the greater proportional change in Ki67 in the group that was also positive for PR (to $\sim 50\%$ of baseline levels) are consistent with expectations: it is known that proliferation is generally higher in ER-negative tumors (6, 16) and that tumors positive for PR as well as ER have a greater likelihood of responding to endocrine therapy (13).

It is possible that the results underestimate the effects that idoxifene would have at steady state. The terminal half-life of the drug is $\sim 5$ weeks$^3$ such that after a median 16.5 days of treatment only approximately half of one half-life would have elapsed. The plasma levels at the time of excision would approximate to only one-fourth those of steady-state levels, and the drug exposure over the preceding 16.5 days would be represented by an exponential function toward

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$^3$ Data on file at SmithKline Beecham.
these levels. Thus, the impact on proliferation is likely to be
equivalent to that which an idoxifene dose of 10 mg/day or
less would achieve at steady state [the pharmacokinetics of
idoxifene being linear (2)]. To have achieved steady-state
levels by 16.5 days in this study would have required a
loading dose of idoxifene substantially above that adminis-
tered previously to humans.

A number of studies have shown that apoptosis can be
induced by estrogen withdrawal or by an antiestrogen, both in
vitro and in animal model systems (10, 11, 17, 18). In an earlier
small study by our group, apoptosis was also found to be
significantly higher in patients treated with ICI 182780 com-
pared with controls; in patients treated with tamoxifen apoptosis
showed a small change with borderline statistical significance
in patients with ER-positive tumors (9). Recently, we also have
shown that idoxifene treatment of estrogen-supported MCF7
xenografts leads to increased apoptosis (12). Thus, the absence
in this study of a significant increase in apoptotic index after
treatment with idoxifene was surprising. There may be a number
of reasons why this change was not observed. It is possible that
the exposure of the tumor to relatively low doses of idoxifene
over the treatment period may be insufficient for any impact on
apoptosis. The use of pretreatment biopsies containing relatively
small amounts of tissue may lead to tumor heterogeneity, influ-
encing the accuracy of the data, particularly for a rare event such
as apoptosis. However, the studies referenced above in which
increases in apoptosis were seen had no greater statistical power
than this study and used relatively similar clinical samples. In
addition, our previously published data on the reproducibility of
measurements using core-cuts showed only a marginally poorer
precision for apoptosis than for Ki67 (14). The data may reflect
the true effect of idoxifene on breast tumors in vivo, i.e., that
despite effects seen in model systems there is no effect on
apoptosis in patients.

As noted above, the measurement of ER and PR content
is of importance when evaluating the likely response to
endocrine therapy. The greater decrease in ER levels in the
idoxifene-treated patients than in the placebo group is con-
sistent with some, but not all, earlier data with tamoxifen (6,
19), but it is not as great an effect as that seen with ICI
182780 (7), which decreases stability of the ER protein (20).
In vitro estrogen deprivation leads to increases in ER in
breast cancer cells because estrogen enhances ubiquitin-
proteasomal degradation of ER (21). This is consistent with
our observations of increased ER levels in MCF7 human
breast cancer xenografts on estrogen withdrawal (11). The
mechanism for the decreased ER levels with idoxifene and

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**Fig. 4** Individual changes in ER H-score for the placebo (left) and idoxifene (right) ER+ groups. Pre, pretreatment; D14/21, 14–21 days of treatment.

**Fig. 5** Individual changes in PR H-score for the placebo (left) and idoxifene (right) ER+ groups. Pre, pretreatment; D14/21, 14–21 days of treatment.
tamoxifen is not known but may also relate to ligand-dependent proteasomal degradation.

The decrease in ER shown in the placebo group emphasizes the importance of placebo controls in this sort of study. This decrease may have occurred as a result of histological fixation differences between core-cuts and excision biopsies. Other possible explanations are that the taking of a core-cut may itself induce a change in ER in the tumor or that systematic differences in scoring between core-cuts and excisions might occur despite efforts to avoid this. A further consideration is that the change in the ER H-score may result from a conformational change in ER induced by the binding of idoxifene, which could influence the binding to antibody.

PR is an estrogen-induced gene, and its expression is considered as denoting an intact estrogen response mechanism (21). By extension, decreases in PR expression may be considered indicative of an antiestrogenic effect as seen with ICI 182780 (7). In contrast, the early increases seen in PR after initiating tamoxifen treatment are considered indicative of an early predominance of an agonist effect of tamoxifen [at least on the PR gene (22–24)], although this does not indicate lack of efficacy; those patients showing an increase in PR (after a median 13 days of tamoxifen) have a greater likelihood of response (23). The trend toward an increase in PR with idoxifene but lack of a statistically significant effect may indicate that idoxifene has some agonist activity on this parameter in the breast, but less than tamoxifen, which is consistent with its lower uterotropic effect than tamoxifen in rodents (1).

Idoxifene was well tolerated, and no major side-effects or changes in laboratory values were observed, consistent with other reports on its clinical usage.

This is only the second report of a randomized biomarker study [the first was the study of ICI 182780 (7)] during a prescribed period of time between diagnosis and the time at which a patient is scheduled for surgery. Medical treatment is not conventionally offered during this time, and it offers the opportunity to assess and compare new drugs once their safety has been established. Importantly, changes in Ki67 over this period by tamoxifen relate to subsequent response to therapy (8). The consistency of the data derived here with those that would be expected of an effective SERM not only supports idoxifene being an effective anti-breast cancer agent, it also supports further exploitation of this clinical scenario with novel therapies.

In conclusion, idoxifene showed a significant antiproliferative effect in ER-positive breast cancer as shown by the decrease in the Ki67 labeling index with no effect in ER-negative cancers. This is consistent with idoxifene being an effective anti-breast cancer agent in ER-positive tumors.

ACKNOWLEDGMENTS

We thank the following investigators who also entered their patients into this trial: Dr. Jacques De Greve, Dr. Gilbert De Wasch, Dr. A. Labrie, Dr. R. Vree, Dr. H. Sloothoorn, Fiona MacNeill, R. J. Sainsbury, Dr. J. Bonnetterre, Dr. L. Beex, and Dr. T. Pienkowski. The centralized pathology review was undertaken by Dr. N. Nasiri.

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